REPORT OF THE STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING PANEL

Volume Two / Part Five

VISION research

A NATIONAL PLAN

1983-1987

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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PREFACE

THIS IS THE Report of the Strabismus, Amblyopia, and Visual Processing Panel, which is Part Five of *Volume Two, Reports of the Program Panels,* of the multivolume report of the National Advisory Eye Council entitled, *Vision Research—A National Plan: 1983–1987.*

The complete National Plan presents a comprehensive and detailed assessment of the current NEI program as well as specific recommendations for program development over the next five years. These include program priorities and projections of resource requirements for each major area of vision research that the NEI supports. Readers desiring additional information should consult the following volumes:

Executive Summary (Overview of the entire Plan.)

Volume One—The 1983 Report of the National Advisory Eye Council (Background, Summary Panel Reports and Resource Requirements, Implementation Strategy, Cross-Cutting Research Areas and Issues, Planning Participants, Planning Strategy and Process).

Volume Two—Reports of the Program Panels

Part One—*Report of the Retinal and Choroidal Diseases Panel*

Part Two—*Report of the Corneal Diseases Panel*

Part Three—*Report of the Cataract Panel*

Part Four—*Report of the Glaucoma Panel*

Part Five—*Report of the Strabismus, Amblyopia, and Visual Processing Panel*

Part Six—*Report of the Panel on Visual Impairment and Its Rehabilitation.*

Volume Three—Support for Vision Research (Data on vision research projects supported by the NEI in FY 1981 and by other government and private organizations in FY 1980).

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SUMMARY

INTRODUCTION

SEEING INVOLVES a series of highly complex events that begin the instant images fall onto the retina and continue until objects are perceived in all their detail, depth, and color. Visual processing is always accompanied by searching and scanning eye movements and is further refined by converging and focusing the eyes onto objects. A disturbance of any of the many parts of this elaborate and precise system can lead to serious visual disturbances, such as amblyopia, visual field defects, strabismus, nystagmus, and myopia. Although disorders of visual processing may not always cause total blindness, they nonetheless may seriously diminish the professional opportunities and the quality of life of those they afflict. And, because these conditions affect more than 10 percent of the population, they constitute serious public health problems.

The National Eye Institute's Strabismus, Amblyopia, and Visual Processing program supports research on the structure, function, and development of the extraocular muscles and those portions of the brain that make vision possible. Such research is directed toward gaining a better understanding of normal vision and the causes of visual deficits and blindness that do not appear to result from specific dysfunction of the eye itself. This program is committed to support research aimed at preventing or treating strabismus (misalignment of the eyes), amblyopia (commonly known as "lazy eye"), myopia (nearsightedness), and neuro-ophthalmological disorders. Understanding visual processing and its disorders requires a working knowledge of the human nervous system and related molecular, genetic, chemical, cellular, and integrative neural processes, as well as overt perceptual responses. Continued advancement of clinical investigation in this field rests upon an improved understanding of basic visual mechanisms; thus, both basic and clinical research are necessary for the development of new methods for diagnosing and treating visual disorders.

Strabismus

It has been estimated that at least 3 to 4 percent of the United States population is born with or develops strabismus during the first six years of life. Many more millions of people in the United States have a manifest or latent eye muscle imbalance. For its victims, strabismus represents much more than a cosmetic problem, because it often causes serious visual problems. People with esotropic strabismus (cross-eye), which is the most common form, often experience a restricted field of vision and loss of binocular function; these problems also occur frequently in people with exotropic strabismus (wall-eye).

About half the children with strabismus tend to use one eye more than the other; if untreated this condition leads to diminished vision in the less used eye, a condition known as strabismic amblyopia. Other children with strabismus alternately use one eye or the other, but do not use both eyes at once. These children lose their ability to fuse images and hence experience impaired depth perception. Both types of visual deficits may create learning problems and job handicaps later in life, particularly in occupations that require fine, manipulative, and binocular skills. It is important to note that congenital disorders of the oculomotor system are occurring more frequently today because a high percentage of premature and "small-for-gestational-dates" infants, who are at greater risk for such disorders, are surviving as a result of improved neonatal care.

Amblyopia

Amblyopia, diminished vision due to disuse of an eye, is a common visual impairment. About half of

all cases of unilateral amblyopia are caused by strabismus. Uncorrected anisometropia, in which the refractive powers of the two eyes are different, is the second most common cause of amblyopia. Another type, called deprivation amblyopia, is caused by insufficient visual stimulation at an early age due, for example, to congenital cataracts. All types of amblyopia, whether unilateral or bilateral, are characterized by a reduction in vision despite optimal eyeglass or contact lens correction and the absence of detectable structural lesions in the visual system. Essentially any long-term visual deprivation that occurs in early life and during a critical period of development may cause amblyopia. It is important to realize that amblyopia may be preventable or curable if contributing visual problems such as strabismus, refractive error, or cataract are corrected early enough. Although amblyopia itself generally does not produce total blindness, studies indicate that the better eye of amblyopic patients may be significantly more susceptible to loss through injury than are the eyes of nonamblyopes.

Ocular Effects of Neurological Disorders

A number of ophthalmological problems are associated with neurological disorders; these include nystagmus (involuntary, abnormal eye movements), optic neuritis (inflammation of the optic nerve), and the ocular effects of nerve palsies, multiple sclerosis, stroke, and brain tumors. Measurements of visual function and/or eye movements are useful in diagnosing neurological dysfunctions and for following their course. Conversely, several neurological disorders clearly cause vision problems, but the public health impact and prevalence of these visual disorders have yet to be measured.

Refractive Errors

Refractive errors represent yet another major public health problem. Approximately 60 percent of all people in the United States wear corrective lenses during all their waking hours, and an estimated 70 million Americans have myopia. At least 90 percent of all individuals beyond age 45 wear corrective lenses at least part-time; this high percentage is due primarily to the onset and progression of presbyopia, which is a diminished ability to focus on nearby objects after age 40.

High degrees of myopia can cause other eye problems, the most serious of which is retinal detachment. Approximately 42 percent of all people who suffer detached retinas are myopic to some degree. The lifetime risk of detached retina (to age 60) is 10 percent for individuals with more than eight diopters of myopia, compared with 0.06 percent for those without myopia. Because approximately 1 percent of the United States population has at least eight diopters of myopia, about 2.2 million individuals are at increased risk of developing retinal detachment. (See also *Volume Two, Part One, Report of the Retinal and Choroidal Diseases Panel,* Chapter 6, "Retinal Detachment and Vitreous Disorders").

PROGRAM STRUCTURE

Research in the National Eye Institute's Strabismus, Amblyopia, and Visual Processing program is divided into three major categories: Amblyopia and Visual Processing; Ocular Motility and Strabismus; and Optics and Refractive Errors, Including Myopia. Within each of these categories, the program is further broken down into subprograms and areas according to the following outline, which is also the basis for the organization of this report.

Strabismus, Amblyopia, and Visual Processing Subprograms and Areas:

1. Visual Processing and Amblyopia
   a. Normal and Abnormal Development (Chapter 1)
      (1) Molecular
      (2) Cell and Systems
      (3) Behavior
   b. Structure and Function (Chapter 2)
      (1) Molecular
      (2) Cell and Systems
      (3) Behavior
   c. Disorders
      (1) Amblyopia (Chapter 3)
      (2) Sensory Neuro-Ophthalmic Disorders (Chapter 4)
2. Ocular Motility and Strabismus
   a. Normal and Abnormal Development (Chapter 5)
   b. Structure and Function
      (1) Conjugate Eye Movements (Chapter 6)
      (2) Vergence and Accommodation (Chapter 7)
      (3) Muscle Structure and Physiology (Chapter 8)
   c. Disorders
      (1) Strabismus (Chapter 9)
      (2) Motor Neuro-Ophthalmic Disorders (Chapter 10)
3. Optics and Refractive Errors, Including Myopia
   a. Optics and Refractive Errors, Including Myopia (Chapter 11)

It is important to note that although this National Eye Institute program is concerned primarily with the human visual system and its disorders, basic knowledge of human visual function and dysfunction has been and will continue to be derived in great part from the investigation of a variety of animal species. Although the visual system of primates most resembles that of humans, many

substantial similarities have been demonstrated between human and other mammalian visual systems. In fact, a significant amount of information relevant to the human visual system has been obtained by studying nonmammalian and even invertebrate systems. Furthermore, it is wise to consider the economic and humanitarian value of reserving primates for those studies of the visual system and its disorders for which other animals or in vitro systems cannot be used.

Continued animal studies, new noninvasive tools and techniques for studying human visual function, and the National Eye Institute's experience in mounting and conducting clinical trials will most certainly facilitate the search for new methods of preventing, diagnosing, and treating human eye movement and visual processing disorders.

Visual Processing and Amblyopia

This part of the program is directed toward an understanding of the development, structure, and function of the visual processing system and its disorders. This includes behavioral, cellular, and molecular studies of the entire visual processing pathway, from the optic nerve through all the visual centers of the brain.

The visual pathway consists of an intricate and well defined set of connections. The normal development of these connections requires both a precise set of genetic instructions and a rich visual experience. A thorough insight into the workings of the visual centers is needed in order to design appropriate methods for preventing or treating amblyopia and other disorders of visual processing.

The nervous system analyzes the complex visual environment by first breaking it down into components contained in the responses of individual neurons and then synthesizing these signals to provide the basis for visual perception. To understand how such visual processing occurs, it is necessary to study the entire visual system, to look at the relationship between the psychophysical capabilities of the system and the biological substrate, and to examine how molecular and cellular processes contribute to the integrative mechanisms of the visual network. New techniques for approaching these problems are being developed that just a few years ago were considered only remote possibilities.

Much of the research that has been done on the visual system has been pioneering work applicable to other sensory and motor systems. The work on the function of central visual pathways has been pivotal to our understanding of the brain as a whole. Further research on the development, organization, and function of the visual system may be expected to have wide-ranging significance for understanding the principles of brain function that could lead to elucidation of the etiology of various neurological and psychiatric diseases, as well as visual processing disorders.

Studies of the normal and abnormal development of the visual processing system complement one another; abnormalities can best be understood when compared with the normal situation, and the study of disorders often increases understanding of normal processes. For example, during periods when the visual system is susceptible to change, visual experience influences the development of sight in the infant by actually inducing changes in structures within the visual pathway; therefore, abnormal visual experience may lead to various sensory disorders. This ability of the visual system to be altered by visual experience provides an opportunity for restoring normal function in the young.

A goal of clinical research in this part of the program is to apply new concepts and facts obtained in the laboratory about normal and abnormal visual processing to the prevention and treatment of such disorders as amblyopia, loss of depth perception and other disturbances of binocular vision, and a variety of sensory neuro-ophthalmic disorders. Amblyopia becomes less susceptible to correction as a child grows older. Therefore, it is essential that it be detected early, that the age range be defined during which disorders of visual processing can be corrected, and that the effectiveness of therapy be evaluated while the visual system is still modifiable.

Ocular Motility and Strabismus

Research in this part of the program is concerned with normal conjugate eye movements (the two eyes moving in the same direction at the same time), vergence (the two eyes moving in opposite directions to look at an object), and accommodation (changes in the shape of the lens to focus on an object); and disorders such as strabismus and various forms of nystagmus that affect eye movements and/or positions. Conjugate eye movements seem to be largely "prewired" (determined by neuronal connections) and are of at least two major types: saccadic, which are fast, sudden refixations of the eyes to a new object of regard, and pursuit, which are following movements exemplified by attention to a ball in flight. Vergence eye movements are also of two major types: convergent, those in which the eyes turn inward (toward the nose) when one looks at a nearby object, and divergent, movements in which the eyes rotate outward when looking at an object located farther away. Vergence eye movements are so complex that they require almost perfect functioning of the entire visual system. A significant malfunction in the focusing of either eye, poor vision, or impaired sensory input will degrade their precision.

The purpose of most conjugate eye movement systems is to prevent excessive image motion on the retina that would impair vision. Disorders of these systems are caused by a variety of neural lesions that interfere with the ability to hold eccentric gaze, to generate pursuit movements, or to produce adequate vestibular compensation for head or body movements; they cause the visual images to move on the retina, thereby interfering with visual function. The resulting visual impairment may be so severe that the affected person cannot read, drive a car, or hold a job. Disorders that involve involuntary eye movements or the vestibular apparatus can also produce illusory movement of the environment and dizziness, which can be incapacitating.

Significant vergence system deficits affect a large segment of the United States population. Estimates range as high as 25 percent of the general population; as many as 15 percent have symptom-producing heterophorias (inability to achieve proper convergence for some distance), up to 5 percent have strabismus, and another 5 percent have fusional vergence anomalies. The associated symptoms include asthenopia (eye strain), diplopia (double vision), suppression (vision occurring mainly or only through one eye), amblyopia, and loss of stereoscopic depth perception. Although accommodative anomalies are uncommon (or at least not commonly recognized) among the young, they are virtually universal among the elderly in whom crystalline lens sclerosis and ciliary body vascular changes lead, inevitably it seems, to presbyopia. For both vergence and accommodation, very little is known about what happens between the retinal neural signal and the final responses of the ocular muscles.

Research on the structure, function, and physiology of both intraocular and extraocular muscles is included in this part of the program. The intraocular muscles are responsible for changes in pupil size and lens shape, whereas extraocular muscles control conjugate and vergence eye movements. Information on these muscles, how they function, and their neuronal connections is clearly essential to an understanding of their normal development, function, or dysfunction.

A major objective of research on strabismus is its improved management. Although empirical knowledge of the surgical treatment of human strabismus is available, understanding of eye movement mechanics and central innervational input remains limited, thus restricting the ability to correct the disorder precisely or even to know the optimum age for correction. Because surgical correction of strabismus is the second most frequent ophthalmological procedure in the United States (83,000 operations each year), maximizing its effectiveness is of the highest public health importance.

Optics and Refractive Errors, Including Myopia

Research in this part of the program deals with the failure of the eye to form a focused image on the retina because of an improper combination of refractive power and spacing of the optical components of the eye. Of particular interest are the development, measurement, correction, and prevention of refractive errors. The basic objectives of such research are to correct, more efficiently and effectively, existing refractive errors and concurrently to identify the mechanisms that cause the development of, or changes in, refractive errors in hope of learning how to prevent them. Types of refractive error include myopia (nearsightedness), hyperopia (farsightedness), aphakia (absence of the crystalline lens), astigmatism (unequal refraction for different visual axes, usually resulting from irregularities in corneal curvature), and presbyopia.

Despite the fact that the optical components of the eye develop and grow at different rates, the combined optical effect of these components generally remains remarkably correct throughout normal development. Characterization of both normal and abnormal ocular growth processes is extremely important in understanding how and why refractive errors develop. Also important are population and epidemiological studies on refractive errors, the development of animal models for these disorders, biomechanical analyses of the forces exerted on the various components of the eye, and biochemical investigation of the ocular tissues that determine the shape and optical characteristics of the eye. Clinical trials may play an important role in evaluating proposed means of controlling the development of refractive errors. (See also, *Volume Two, Part Two, Report of the Corneal Diseases Panel,* Chapter 3, "Refractive Problems and Contact Lenses").

ORGANIZATION OF THE PLAN

Each chapter in this report begins with an introduction that highlights the importance of the research field or disorder it addresses. This is followed by a list of subprogram objectives, an overview of current research support, a review of recent research accomplishments, and a discussion of current research needs and opportunities. This analysis culminates in a list of the Panel's recommendations for the Program Base and for Program Development Priorities within the subprogram.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in

which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Each chapter concludes with a table that shows the number and dollar amount of research grants supported in each of these areas in FY 1981 and the number and estimated costs of projects the Panel recommends for funding by FY 1983. For a detailed discussion of the planning process used to develop these recommendations see *Volume One, The 1983 Report of the National Advisory Eye Council.*

PROGRAM GOALS

- To understand the mechanisms controlling the development of the central visual system, including its modifiability by endogenous and exogenous factors.
- To develop clinically useful, noninvasive methods of assessing visual capacities in adults and, especially, infants and young children.
- To define at molecular, cellular and systems, and behavioral levels the normal and abnormal processing of visual information.
- To use this knowledge to devise better strategies for preventing and treating amblyopia and other neurosensory disorders.
- To understand the development, structure, and function of the neural and muscular systems that control eye movements, including the variety of subsystems involved in fixating and tracking objects and the interaction of the visual and vestibular sensory sytems.
- To understand the accommodative process and its relationship to vergence eye movements, especially during infancy and in early childhood disorders of ocular motility.
- To devise better surgical, pharmacological, and behavioral strategies for managing strabismus and other neuro-ophthalmological disorders of ocular motility.
- To determine the etiology and course of development of myopia and other refractive errors in order to prevent their occurrence or progression.

OVERVIEW OF CURRENT RESEARCH SUPPORT

In the United States support for research on central visual processing, eye movements, and disorders thereof is provided mainly by the National Eye Institute. In FY 1981, the National Eye Institute supported 268 grants, mainly for basic research, on these subjects at a total cost of more than $22 million. Additional support for research on basic visual mechanisms is provided by the National Institute of Neurological and Communicative Disorders and Stroke, the National Institute of Mental Health, and the National Science Foundation. Some studies of visual development are supported by the National Institute of Child Health and Human Development. The Department of Defense supports research on basic perceptual processes and their application to combat or flight situations. Overall, however, very few clinical studies of central visual processing or eye movements are being supported by any agency.

RECENT ACCOMPLISHMENTS

Visual Processing and Amblyopia

Reliable data on the visual capabilities of infants and young children have been difficult to obtain because infants are nonverbal and generally have short attention spans. Such information has become available only in the last few years, largely through preferential looking methods and noninvasive electrophysiological techniques such as visually evoked potentials. Studies show that a baby's visual acuity develops rapidly during the first year of life and approaches normal adult values during the second year. Stereopsis is present by about 14 weeks and undergoes striking development between 15 and 20 weeks. Such findings are having considerable impact on therapeutic approaches to strabismus, especially in deciding the age and procedures for optimum correction of this disorder. Other visual

capabilities, including contrast sensitivity and color vision, are being studied by similar methods.

A crucial concept in understanding the maturation of the human visual system is based on animal experiments that demonstrate the existence of a "critical period," which is a limited time during development when many characteristics of the infant's visual system are refined and modified by visual experience. Cellular studies indicate that some of the response properties of cells to specific types of stimuli, binocular interactions, and the columnar architecture of the visual cortex may be based on innate characteristics of the cells themselves; however, normal visual experience is also important for the full maturation of the visual system.

Previous suggestions of rigid cell-to-cell interactions have been replaced by the idea of connections that can be modified in the growing animal and that may change after surgical alteration or deprivation. For example, it has been known for some time that animals reared with an eye closed during the first few months of life experience profound changes in their visual cortex. Research with infant monkeys shows that visual deprivation from birth results in marked functional changes in the visual system within days. Animals that are subjected to prolonged periods of monocular visual deprivation at a young age experience functional blindness in the occluded eye. Such deprivation apparently produces abnormalities in the afferent fibers from the lateral geniculate nucleus located in the midbrain, that would normally provide the visual input to the visual cortex, at the back of the brain. For animals experiencing monocular deprivation, most of the cortical cells that normally are activated by stimuli delivered to either eye are no longer driven by input to the deprived eye. The defects caused by monocular deprivation can be reversed after eye opening by closing the other eye, but this type of cortical plasticity (ability to change or adapt) persists only through the first few months after birth.

Other studies show that a deprived eye can regain some of its ability to drive cortical cells if the normal eye is removed. This finding suggests that the defect is partly due to suppression of deprived cortical cells by input from the normal eye. Experimental monocular eyelid closure has become a model for deprivation amblyopia and is being studied to determine the relative contributions of experience and heredity in the development of the entire nervous system.

Synaptic plasticity in the geniculostriate pathway (the portion of the visual pathway that extends from the lateral geniculate nuclei to the visual cortex, which is located at the back of the brain) may be influenced by local levels of catecholamines. A toxic analog of the neurotransmitter norepinephrine seems to block the cortical defects in cats, described above, that occur when they are reared with one eye sutured closed. The effect of the toxic analog apparently can be counteracted by microperfusion with norepinephrine. Studies suggest the possibility of pharmacologically extending the critical period of visual development, or of conferring plasticity onto the adult visual cortex for a brief time, so that the harmful effects of visual deprivation can be minimized or reversed.

Research on the development of visual processing in humans is furthered by studies in lower vertebrates which have larger neuronal cells and simpler systems and whose visual system cells continue to increase in number, grow, and differentiate in adulthood. These features permit examination of the molecular and cellular basis of visual system development in great detail. One important finding originally made in lower vertebrates is that the ultimate pattern of innervation becomes less diffuse and more restricted as the animal develops. This finding is serving as a basis for the design of new experiments to learn more about the determinants of neural development.

Accumulating evidence shows that the nervous system analyzes the complex visual environment by first dividing images into components to which individual neurons respond and then assembling these signals to provide the basis for perception. Anatomically and functionally distinct pathways, called X, Y, and W, from the retina to the cortex have been identified. Many lines of investigation indicate that neuronal cells of a given type are arranged in the cortex in clusters or columns. These columns have been demonstrated by techniques such as electrophysiology, fiber staining, transneuronal transport of radiolabeled amino acids, and selective uptake of ^{14}C-2-deoxyglucose. Studies have shown that these cell columns respond differently to different types of ocular inputs, orientation, or other receptive field properties. For example, some columns are more responsive to horizontal light bars, others to vertically oriented bars. Cortical columns also differ in their responsivity to large or small stimuli, to light or dark stimuli, or to the direction in which a stimulus is moving. Some cells respond to stimuli in a complex manner that depends on several factors, such as size and location.

Other data indicate additional complexities in the organization of the brain, even within functionally distinct cortical pathways. Patchy distributions of nerve terminals occur within several cortical pathways, and intracellular staining techniques have demonstrated complex interconnections within a single cortical area, which are formed by individual neurons that spread widely through that area. These discontinuous patches, columns, and modules of the cortex undoubtedly play a major role in the func-

tioning of the brain, and research is underway to examine their functional roles.

Recent work has emphasized the role of inhibition among neurons as a means to regulate cortical processes. For example, visual input from one eye can inhibit the response of the other eye. Other studies of interactions among neurons have led to significant advances in understanding how contrast, contour, brightness, and color are encoded at the cellular level and have helped to define the neural interactions that are involved.

Significant advances have been made in identifying neurotransmitters in the visual system. The transmitter that has been most clearly identified in the visual cortex is gamma-amino butyric acid (GABA), which seems to be employed by the smooth stellate cells, a cell type thought to mediate inhibition in the cortex of responses to visual stimuli. An inhibitory role for GABA is also suggested by the changes in the physiological properties of visual cortical cells that are caused by iontophoresis of bicuculline, an antagonist to GABA. These results indicate that local inhibitory mechanisms may be important for the specificity of receptive field properties, such as directionality and orientation.

Historically, behavioral investigation has been an important functional approach to the study of visual processing; it provides data on the overall capabilities of the human visual system that can be evaluated and compared with the results of other approaches, such as electrophysiological measurements. In addition, behavioral investigation enables one to define what constitutes normal vision and to describe and quantify how various diseases affect visual performance.

The concept that the visual system processes various types of information through separate channels has served as a basis for psychophysical studies of color vision, in an approach that parallels the neuroanatomical and neurophysiological studies described above. Visual information appears to be transmitted separately by chromatic and achromatic channels that are initiated in the retina but elaborated more centrally in the visual system. Studies of individuals with abnormal color vision are making it possible to understand better normal color vision and its underlying physiology.

It has been known for more than a century that humans are capable of making finer spatial distinctions than would be expected from the size of their photoreceptors. Recent studies of this phenomenon, called hyperacuity, are revealing additional complexities in visual processing in the brain. New modes of analysis are making use of intermittently exposed stimuli, that is, two different stimuli that are shown sequentially to test the resolution of the visual system.

For more than a decade, random-dot stereograms have been the major tool for testing stereopsis. Recently, improved techniques and targets have been designed that exclude monocular clues so that stereoacuity can be measured more precisely and reliably. New techniques to examine the summation of signals from the two eyes and the transfer of after-effects from one eye to the other are being used to outline the convergence of pathways from the two eyes. These should help resolve long-standing questions about the factors that determine whether an individual will experience fusion or diplopia (double vision).

The improved diagnosis and treatment of amblyopia is an important research goal. Visually evoked cortical responses and forced choice preferential looking techniques are promising means of diagnosing amblyopia in infants and following the course of therapy. Results indicating that elements in the cortex and lateral geniculate nucleus vary in their susceptibility to visual deprivation may help explain the diversity of clinical, electrophysiological, and psychophysical responses seen in human amblyopes. The early detection of significant refractive errors may prove to be the key to early identification of the actual or potential amblyope.

Neurogenic impairment of vision occurs in a variety of diseases, some of which are commonly encountered in ophthalmic practice. Lesions in the optic nerve, chiasm, tract, and geniculostriate pathway produce characteristic alterations in visual acuity or visual field that may permit the clinician to localize the malfunction. Identification of the disease responsible for a lesion has sometimes been difficult; however, the visually evoked response is proving useful for the differential diagnosis of optic neuritis, multiple sclerosis, and ischemic optic neuropathy.

In addition to diagnostic advances, progress has also been made in determining the etiology of one form of optic neuropathy, papilledema. This disorder, which is a swelling of the optic nerve, has been found to result from a damming of axoplasmic flow (movement of substances through the axons of nerve cells) and not from accumulation of intercellular fluid, as was previously thought. Development of treatment strategies can now be concentrated more efficiently on intracellular mechanisms.

Ocular Motility and Strabismus

An understanding of the structure and normal development of the systems that create or regulate eye movements is, of course, essential for devising treatments for eye movement disorders. The application of control systems analysis to the oculomotor system has directed attention to the most important aspects of the system's behavior. Preliminary studies

in human infants suggest that the vestibulo-ocular system matures much earlier than other oculomotor systems, but that maturation may be significantly delayed in premature infants or those who are "small-for-gestational dates." Whether these delays cause long-term disorders of ocular vestibular function has not yet been determined, but preliminary data suggest that specific patterns in delayed maturation are associated with some forms of horizontal comitant strabismus.

The arrangement of the extraocular muscles is incomplete at birth; the location of normal muscle insertion in relation to the limbus continues to change during the first several months of life. This observation has obvious significance for the ophthalmic surgeon performing early strabismus surgery.

Knowledge of the central neural circuits that control eye movements increased rapidly in the 1970s through the development of techniques for recording from neurons and fibers in alert animals able to make normal eye movements. New anatomical tracer techniques have led to the discovery of previously unknown areas of the brainstem and cerebellum that influence ocular motility. In turn, these approaches have led to a good understanding of some but not all aspects of the normal behavior of eye muscles and their motor neurons. The definition of at least two separate anatomic systems involved in optokinetic nystagmus in monkeys has provided interesting insights into several disorders of vision. Furthermore, new knowledge of the oculomotor functions of the superior colliculus and frontal eye fields may help in understanding the relationship between visual perception and muscle action.

The importance of studying neurotransmitters in the oculomotor system was dramatically emphasized by the recent discovery that the drug baclofen, a synthetic analog of GABA, stops periodic alternating nystagmus, a disorder in which jerk nystagmus to the left is replaced by nystagmus to the right about once every two minutes, thereby degrading vision to the point that makes reading impossible. Baclofen stops these ocular oscillations and permits normal visual function. This discovery was facilitated by a control systems analysis of the oculomotor system.

Studies that helped delineate surgical planes, fascia, and extraocular muscle anatomy have helped eye surgeons perform accurate and complication-free strabismus surgery. Computer techniques that utilize both eye movement modeling theory and data on the results of strabismus surgery have also been used to assist in surgical decision-making. New suture materials and needles specifically designed for strabismus surgery have been developed, and the spring-back balance test provides a new way of assessing mechanical muscle and orbital factors during surgery.

Botulinum toxin has been used to treat strabismus in patients in whom surgery is contraindicated. This toxin has been injected into the antagonist of a paralyzed extraocular muscle under electromyographic control to diminish or eliminate, at least temporarily, the deviation and to prevent contracture of the antagonist muscle. In some cases, treatment of eye alignment with botulinum toxin has produced fairly long-lived results. In other cases, administration of botulinum toxin has made additional treatment of strabismus easier.

The use of animal models continues to be important for studies of strabismus. The recent identification of a strain of monkey with a type of naturally occurring strabismus, somewhat comparable to that found in humans, should aid studies aimed at a better understanding of this disorder.

Major clinical advancements have been made through the utilization of quantitative eye movement recording (oculography) in patients with abnormal eye movements. The simultaneous recording of head and eye movements in patients with clinical oculomotor or neuro-ophthalmological disturbances is another recent advance that continues to bear fruit. This approach is a more realistic way of studying eye movement disturbances because, in the real world, heads move freely and are not fixed. Case reports of simultaneous head and eye recordings in patients with congenital nystagmus (abnormal eye movements) and spasmus nutans (head nodding associated with abnormal eye movements) have provided information that was totally unexpected from clinical observation alone.

Optics and Refractive Errors, Including Myopia

Experimental studies of myopia have been greatly furthered by the finding that lid closure in young monkeys leads to the development of axial myopia. Similar observations have been made with lid closure in the tree shrew and with field-restricting blinders in the chicken. There has also been a report of several cases of monocular axial myopia in human infants associated with neonatal lid closure, caused by problems such as eyelid damage or congenital defects, and the possible factors that may produce the phenomenon have been investigated. With the upsurge of interest in myopia, major activity, both in basic research and clinical investigation, is beginning.

RESEARCH NEEDS AND OPPORTUNITIES

Visual Processing and Amblyopia

New and more practical techniques and instrumentation for determining visual function in infants need to be developed and tested. The two principal existing techniques, the preferential looking method and the recording of visually evoked potentials, need to be compared directly with one another.

Much of the research needed on normal visual development is molecular in nature. It is necessary to know, for example, the molecular factors involved in the differentiation of nerve cells into nuclei and layers, their migration to their final positions, and the establishment of specific neuronal connections. It may be possible to identify specific cell markers and use them to follow cell maturation as they achieve their final location and shape. It should be possible ultimately to characterize the molecules reponsible for determining the fates of cells and to elucidate the roles of competition, inhibition, biogenic amines, peptides, growth factors, visual experience, inheritance, and temporal and spatial factors on development. Once embryogenesis is understood, regeneration of optic axons in older children and adults may become possible.

Behavioral research will be beneficial both for its value in providing a framework for understanding the physiology and anatomy of the visual system and for its potential use in devising new diagnostic tools and methods of treating visual disorders. The concept of sensory "channels," as a basis to interpret results of behavioral studies on visual processing, needs to be explored further in relation to the underlying neural mechanisms. Behavioral results need to be correlated with those from neurochemical, neurophysiological, and neuroanatomical studies. Psychophysical studies based on this concept are likely to continue to yield important information about specific neuronal mechanisms. For example, a given narrow band of spatial frequencies is processed independently of other spatial frequencies; changes in size are processed independently of sideways motion, contrast, and intensity changes; and there may be separate channels for other processes such as color, orientation, and flicker.

Studies of the cellular and integrative mechanisms in visual processing need to be continued at higher levels of resolution (for example, micro-scale connections between neurons) using new techniques such as intracellular marking, cross-correlation of results with different markers, tissue slices, and cultured dissociated neurons. Insights from studies at the cellular level need to be related to the functioning of the visual sensory system as a whole. This should include further analysis of the functional cell classes within the cortex and determination of how each contributes to form vision, eye movements, and other visual functions. At the molecular level, studies are needed first to identify the transmitters that operate at various levels in the visual pathway and then to develop appropriate antagonists for use in pharmacological studies of disorders involving abnormal transmitter function.

More clinical and basic research is needed on amblyopia. In particular, further research is needed into techniques for the clinical investigation of amblyopia. More specific psychophysical tests could assist in the detection and differential diagnosis of amblyopia, as well as other ocular or neurological disorders. Methods are needed to measure visual acuity reliably and simply in children ages 1 to $3\frac{1}{2}$, in whom amblyopia is difficult to diagnose but more responsive to treatment. Research is needed on devising and evaluating techniques for large-scale screening programs to detect amblyopic and potentially amblyopic children at an early age. Additional studies are needed on the natural history of amblyopia; in particular, the ages at which children are susceptible to this disorder or respond to therapy need to be determined.

Refinement of animal models of visual deprivation and amblyopia that simulate the human situation more closely is desirable. For example, techniques are needed that produce relatively less severe reductions in visual acuity and preserve some degree of binocularity.

Epidemiological studies of neuro-ophthalmic disorders are needed on a national and worldwide basis to assess their impact on public health. Primate models of optic neuropathies are needed for studies of the cellular basis for the changes in electrophysiological responses that are seen in these disorders.

Ocular Motility and Strabismus

Another important subject requiring further investigation is the sensitivity of the infantile visual system to strabismus. The critical period during which misalignment of the visual axes or ocular opacities can cause permanent defects in binocular vision needs to be defined better to determine the urgency with which individual eyes must be corrected by optical or surgical means to permit normal binocular functions. In addition, further evaluation is needed of how effectively occlusion of the dominant eye at different times can reverse the effects of visual deprivation on the retina, the visual cortex, and the X and Y cell populations of the lateral geniculate nuclei.

There have been few developmental studies of the human oculomotor system, particularly of the normal embryogenesis of extraocular muscles, cranial nerves, or intracerebral pathways. More basic and

clinical research on the maturation of normal systems is essential for a better understanding of human developmental oculomotor defects. Techniques are needed for the quantitative analysis of eye movements in newborn infants that will permit studies of how delays in the maturation of oculomotor subsystems are related to later disorders of ocular motility. Studies are also needed of how normal infants establish eye alignment and fusion, as well as the adaptive oculomotor strategies that permit infants to compensate more rapidly for visual cortical damage than adults.

Tests should be devised to distinguish between the pursuit and optokinetic oculomotor subsystems. Especially needed are sensitive tests that could be used in the clinic to detect oculomotor abnormalities.

Research utilizing anatomical tracers in combination with recordings from the neurons of alert animals, especially primates, needs to be continued in order to understand the oculomotor circuits in the brainstem, cerebellum, and cerebral cortex.

Although research has led to an understanding of some aspects of eye movements, much additional work is needed. For example, progress in understanding the vestibulo-ocular reflex has been excellent, especially in describing the behavior of the vestibular apparatus, but the contributions of the reticular formation (in the midbrain) and the flocculus (in the cerebellum) are still unknown. Some knowledge exists of the optokinetic system in animals, such as the rabbit, although many aspects of its central connections from the accessory optic system to the vestibular nuclei and the role of the transcerebellar pathways remain to be clarified. Understanding of the saccadic and pursuit systems is meager. The anatomical and functional relationships between motoneurons and a few immediately premotor cell types that mediate saccades or pursuit movements are known, but more central circuitry remains poorly understood.

The effectiveness of new surgical, pharmacological, and other nonsurgical treatments of strabismus needs to be evaluated. The development of appropriate animal models of this disorder should greatly aid understanding of the sensory and motor deficits involved. One of the problems in the clinical management of human strabismus is that various authorities and medical centers approach the problem in their own way, using past experience as the primary guide to the proper therapy. This leads to reports of the success of an individual treatment technique that are based on experience with limited numbers of patients who have been treated and evaluated in a relatively noncontrolled manner. The result has been the development around the country of various "schools" of management, each with trainees and disciples believing that their approach is best. Multicenter controlled studies of the treatment of strabismus are needed to define the best approach.

Progress is being made in the improved quantification and analysis of eye movements during neuro-ophthalmological examinations. Some neurological diseases, myasthenia gravis for example, can now be diagnosed with a reasonable degree of certainty by eye movement recordings. Such recordings can also facilitate the diagnosis of multiple sclerosis. In addition, results from basic research are being integrated into models that give clinicians working hypotheses to explain the basis of oculomotor disorders. Continued research is needed to define eye movements quantitatively in a variety of central and peripheral neurological diseases. This will facilitate diagnosis of these disorders, assist in designing treatments for them, and provide explanations of their basis.

The cost effectiveness of computerized analysis of oculomotor functions needs to be compared with that of analysis by trained ophthalmologists.

Optics and Refractive Errors, Including Myopia

Research is needed to design better mass screening techniques for refractive errors. Particularly needed is the development of techniques that can be used with small children. More extensive epidemiologic studies are needed to identify hereditary and environmental factors associated with the development of refractive errors. The following questions, among others, should be addressed: Does the accommodation and/or convergence associated with reading lead to, or aggravate, myopia? Do unusual diets or climatic conditions favor, or prevent, the development of refractive errors? Are any systemic diseases associated with the development of refractive error? Does the wearing of spectacles or contact lenses alter the progression of myopia? Are certain forms of glaucoma or strabismus associated with myopia? Which diseases of the eye and ocular adnexa affect the size of the eyeball?

Improved animal models are needed for the study of refractive errors, especially myopia, to allow investigation of possible causative factors and preventive measures. Carefully controlled clinical trials should be performed where appropriate to evaluate proposed measures for preventing the development of myopia.

RESEARCH TRAINING NEEDS

The field of developmental biology, including that of the visual system, has expanded rapidly in the last decade, and major breakthroughs have occurred. A basic understanding of normal maturation of the sensory and motor systems is obviously important for gaining a better comprehension of the factors responsible for abnormalities in these systems. However, the present skills, techniques, and approaches of basic scientists involved in developmental biology research have generally not been understood by the clinical community or applied to clinical problems. Therefore, a major commitment should be made to bring clinicians who are interested in developmental biology into the field of pediatric ophthalmology. Research fellowship programs in this discipline should be encouraged where there are appropriate personnel to provide adequate training.

Because improved and more clinically useful methods should be devised for measuring visual acuity and other functions, particularly in infants and young children, additional biomedical engineers, ophthalmologists, and optometrists are needed to collaborate with psychophysicists in designing such tests.

Improved methods are also needed for the early detection of strabismus and the identification of individuals at risk of developing this disorder. This will require additional research ophthalmologists knowledgeable about strabismus, biomedical engineers and computer specialists to design improved systems for strabismus screening, as well as geneticists and epidemiologists familiar with strabismus and other eye problems to assess the frequency, distribution, and possible causes of strabismus. Investigators trained in ophthalmology and epidemiology who are knowledgeable about clinical trials will be needed to evaluate the various strategies and timings of strabismus treatment that are now being used throughout the country. Pharmacologists will be needed to devise possible drug treatments or treatment aids that would be useful for managing strabismus, particularly in situations where surgery is contraindicated.

Meeting the needs for improved eye movement recording techniques will require additional biomedical engineers and computer scientists as well as neuro-ophthalmologists trained to perform research on the effectiveness of these techniques. Neurophysiologists and neuroanatomists will be needed to elucidate the neural mechanisms involved in visual processing and in eye movements; better understanding of the neural defects underlying these disorders is likely to lead to improved diagnostic and treatment regimens.

Research veterinarians will be needed in all areas of investigation to develop and evaluate improved animal models that more closely resemble human strabismus, amblyopia, myopia, and oculomotor disorders.

It is clear that a multidisciplinary effort involving cooperation between well-trained basic and clinical researchers is likely to provide the most dynamic and useful approach to understanding the function of the human visual system and solving important clinical problems.

Considerable training is required to raise the complement of qualified clinicians who will apply for research grants in *all* the important research areas of the Strabismus, Amblyopia, and Visual Processing program. Furthermore, clinical research training support should be directed toward increasing the limited number of institutions where clinical research is performed and where individual clinical investigators are trained.

SUMMARY OF 1983–1987 RECOMMENDED PROGRAM DEVELOPMENT PRIORITIES

Visual Processing and Amblyopia

- Study the development of the visual system in human infants by devising noninvasive methods and using them to follow the clinical course of disorders after medical or surgical treatment.
- Investigate the pre- and postnatal development of the visual system at molecular and behavioral levels; analyze the effects of visual deprivation and abnormal stimulation on visual function and development.
- Identify neurotransmitters, peptides, and other chemicals important in the signaling between cells in the visual pathways, and in cell specificity and function.
- Further map and analyze the large number of neural areas that are important in the visual process and relate single cell activity with behavioral responses in alert primates.
- Develop methods for large-scale screening and improved procedures for clinical evaluation of vision in very young children to detect abnormalities at an age when treatment is most likely to be effective.

- Characterize better the nature of amblyopic vision, particularly with respect to prognosis for successful treatment. Study the natural history of amblyopia, with special attention to defining the age limits of susceptibility to visual deprivation and the critical period or age for most effective treatment.
- Devise, test, and evaluate better techniques for treating amblyopia.
- Study neurogenic sensory disorders, including the optic neuropathies, by epidemiological, electrophysiological, psychophysical, and histopathological techniques.

Ocular Motility and Strabismus

- Develop recording techniques to study normal and abnormal development of eye movement patterns quantitatively in infants and young children and to improve the diagnosis of strabismus and a variety of central and peripheral neurological diseases.
- Evaluate the adaptive oculomotor plasticity of human infants and young animals in response to disorders of the visual and oculomotor systems, including the cerebellum.
- Describe, at molecular, cellular, and behavioral levels, the development of the oculomotor system, including the extraocular muscles, sensory inputs, and the cerebellum.
- Use model systems in the laboratory to develop and test hypotheses to explain eye movement disorders seen in the clinic.
- Identify the neurotransmitters of the oculomotor system and study how drugs affect them.
- Study the mechanisms of accommodation and vergence, including the stimuli for these processes, response characteristics, interactions and plasticity of the systems, and their anatomy and physiology.
- Conduct clinical investigations of surgical and nonsurgical treatments for strabismus.
- Continue genetic and epidemiologic studies of risk factors for strabismus.
- Develop appropriate animal models of strabismus as aids to understanding the sensory and motor deficits in this disorder.

Optics and Refractive Errors, Including Myopia

- Study the etiology and mechanisms of myopia, using animal models as well as physiological and morphological approaches.
- Conduct epidemiological studies and controlled, well-designed clinical trials of available or proposed treatments for myopia.
- Develop mass screening methods and special purpose instruments for detecting refractive errors.

IMPLEMENTATION OF THE PLAN

The individual, investigator-initiated, NIH research project grant continues to be the National Eye Institute's predominant and highest priority funding mechanism. Therefore, the successful implementation of the recommendations of the Strabismus, Amblyopia, and Visual Processing Panel, as well as those of the other Panels that have contributed to *Vision Research—A National Plan: 1983–1987,* will depend largely upon investigators submitting grant applications for research in the scientific areas the Panel has identified for emphasis. Because scientific merit, as evaluated by the traditional NIH peer review system, will continue to be the principal determinant of which approved grant proposals the NEI will fund, those approved applications having the best "priority" scores assigned by NIH initial review groups will be funded. Applications with mid-range scores will be paid as funds are available; however, some may be specifically designated by the Council as having "High Program Relevance" (that is, fulfilling one of the Plan's recommendations, especially in an area of research considered to be underfunded), and are recommended for placement in a more favorable position for funding. Applications with poorer scores will not be funded—even if they propose research on a topic the Panel has judged to be in need of additional or new support (Chart).

By using such a system, NEI encourages scientific excellence, innovation, and creativity while carrying out its mission of supporting research aimed at alleviating blindness and visual disability. The National Advisory Eye Council will monitor the responses of the research community to the recommendations in the Plan as well as new research advances and developing opportunities, and recommend to the NEI staff on a regular basis what further implementation measures or changes in program priorities may be required. For further discussion of the Plan's development and implementation, see *Volume One, The 1983 Report of the National Advisory Eye Council.*

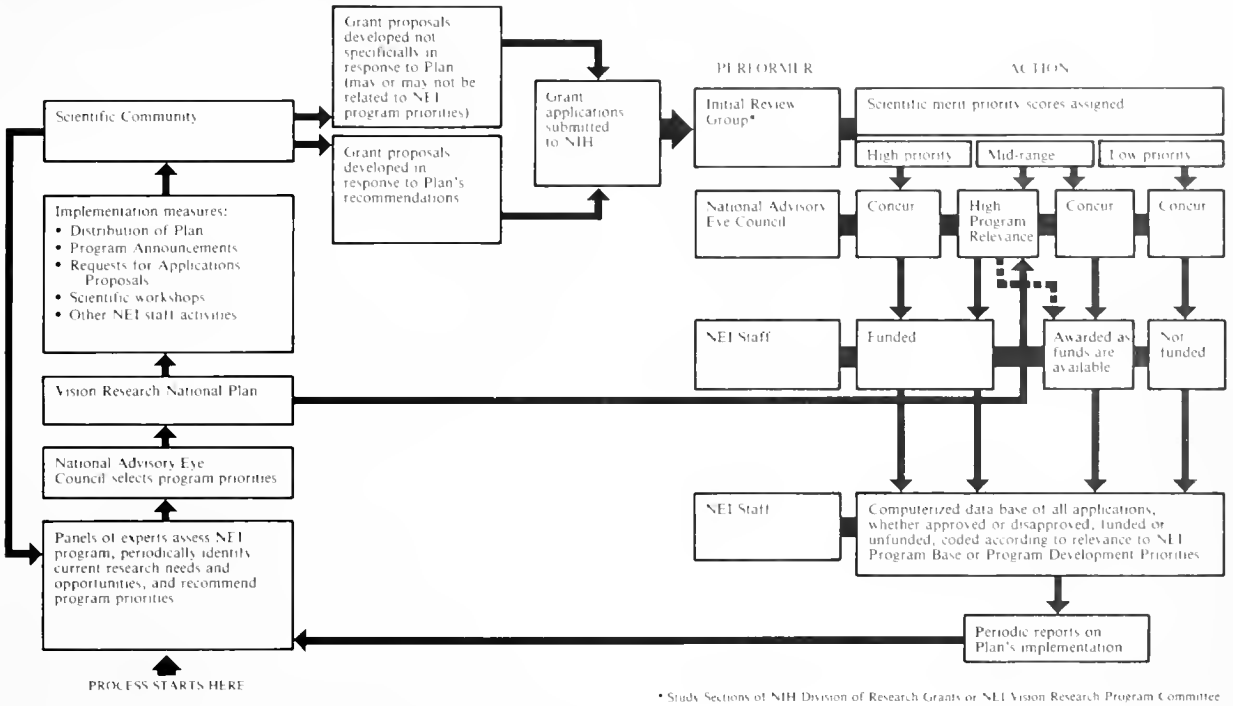

CHART. National Eye Institute Program Planning System. Both the NIH scientific merit priority scores and the program priorities established in the National Plan help determine which grant applications NEI will fund. All applications with high scientific merit priority scores are funded regardless of their relevance to program priorities. Some applications with mid-range scores and judged to be highly relevant to program priorities are singled out and placed in a better funding position than they would have been on the basis of the score alone.

RESOURCE REQUIREMENTS

The following table presents a summary of the Panel's estimates of the number of grants necessary to carry out its recommendations for each of the Strabismus, Amblyopia, and Visual Processing subprograms in FY 1983. The actual number and cost of grants funded in each subprogram in FY 1981 (the base year of the Plan) are shown in the first column. The second column indicates the number of additional (or fewer) grants the Panel believes should be funded in each subprogram through the end of FY 1983, based on an analysis of current research and of future needs and opportunities. The total number of grants for FY 1983 for each subprogram indicated in the third column is the estimated sum of new and continuing awards to be made in that year along with an estimate of their cost.

For example, the first line of the table shows that 19 grants were actually awarded in FY 1981 for molecular studies relating to "Normal and Abnormal Development" of visual processing. Because about one-third of all NEI grants terminate in any given year, in making its estimates for 1983 the Panel assumed that about 6 of the 19 projects funded in FY 1981 would terminate in that year, thereby making funds available for new or renewal grants in this subprogram in 1982 and that another 6 would terminate in that year. The Panel then judged that an additional six grants would be required by 1983 to meet its recommendations in this subprogram. Therefore, of the total of 25 projected awards in this subprogram for FY 1983, approximately 7 would be ongoing and 18 would be new or renewal awards to be funded during FY 1982 and 1983. Thus, even in those subprograms for which the Panel projected fewer grants by FY 1983 than in FY 1981, the potential still exists for the award of new research projects in areas indicated for emphasis.

The actual number of grants funded in these areas may of course be either more or less than these projections indicate, depending on the quality, kind, number, and costs of the grant applications NEI receives and the actual availability of funds. Concerning funding, it must be emphasized that the six Panels' dollar estimates for FY 1983 do not necessarily indicate what the actual National Eye Institute extramural research budget will be for that year. However, because the Panels' estimates are based upon detailed documentation of projected research needs and costs, it is hoped that those in the Executive and Legislative branches of the Government who make the final decisions concerning the NEI budget will use them in making informed judgments about the resources required for the support of vision research. In making these estimates the Panels took into account the following factors for each category of research considered:

- Degree of relevance to the program's goals and objectives
- Current level of support by NEI and other organizations
- Recent research accomplishments
- Potential for future development
- Availability of trained manpower
- Likelihood of significant progress over the next three to five years.

The Panel recognizes that in addition to scientific judgments, social, economic, and political considerations will shape the final NEI budget for each year. Therefore, no attempt has been made in this report to make detailed resource estimates beyond FY 1983, although the Council has projected an overall budget for the NEI through FY 1985 *(Volume One)*. The Panel understands that in the future, the Council, with the assistance of scientists knowledgeable in areas of research supported by the NEI, will provide more detailed estimates for the remaining years of the Plan based on actual budgetary experience and ongoing analyses of research progress. In this way the Plan will be modified as necessary on a year-to-year basis.

At the end of each chapter in this report, subprogram tables show how the estimates shown in the following summary table have been derived from estimates for each research category included in each subprogram's Program Base and the Program Development Priorities.

SUMMARY RESOURCE TABLE

(Dollars in Thousands)

Subprograms/Areas	FY 1981 Grants* Cost		NAEC Recommendation FY 83 Add. Grants Cost		Total Grants Cost**	
1. VISUAL PROCESSING AND AMBLYOPIA						
a. NORMAL AND ABNORMAL DEVELOPMENT						
(1) Molecular	19 $1,675	(7%)	6 $775	(7%)	25 $2,450	(7%)
(2) Cell and Systems	51 $4,682	(19%)	−7 −$370	−(8%)	44 $4,312	(12%)
(3) Behavior	12 $832	(4%)	4 $736	(5%)	16 $1,568	(5%)
Subtotal	**82** **$7,189**	**(30%)**	**3** **$1,141**	**(4%)**	**85** **$8,330**	**(24%)**
b. STRUCTURE AND FUNCTION						
(1) Molecular	6 $579	(2%)	11 $1,087	(13%)	17 $1,666	(5%)
(2) Cell and Systems	62 $5,212	(23%)	−1 $766	−(1%)	61 $5,978	(17%)
(3) Behavior	38 $2,779	(14%)	−6 $357	−(7%)	32 $3,136	(9%)
Subtotal	**106** **$8,570**	**(40%)**	**4** **$2,210**	**(5%)**	**110** **$10,780**	**(31%)**
c. DISORDERS						
(1) Amblyopia	9 $646	(3%)	15 $1,706	(18%)	24 $2,352	(7%)
(2) Sensory Neuro-Ophthalmic Disorders	1 $74	(1%)	7 $710	(8%)	8 $784	(2%)
Subtotal	**10** **$720**	**(4%)**	**22** **$2,416**	**(26%)**	**32** **$3,136**	**(9%)**
Total	**198** **$16,479**	**(74%)††**	**29** **$5,767**	**(35%)**	**227** **$22,246**	**(64%)**

SUMMARY RESOURCE TABLE
(Dollars in Thousands)

Subprograms/Areas	FY 1981 Grants Cost*		Panel Recommendation FY 1983 Add. Grants Cost		Total Grants Cost**	
2. OCULAR MOTILITY AND STRABISMUS						
a. NORMAL AND ABNORMAL DEVELOPMENT	5 $439	(2%)	12 $1,227	(14%)	17 $1,666	(5%)
b. STRUCTURE AND FUNCTION						
(1) Conjugate Eye Movements	39 $3,277	(15%)	6 $1,133	(7%)	45 $4,410	(13%)
(2) Vergence and Accommodation	6 $384	(2%)	7 $890	(8%)	13 $1,274	(4%)
(3) Muscle Structure and Physiology	4 $347	(1%)	2 $241	(2%)	6 $588	(2%)
Subtotal	**49** **$4,008**	**(18%)**	**15** **$2,264**	**(17%)**	**64** **$6,272**	**(19%)**
c. DISORDERS						
(1) Strabismus	9 $618	(4%)	15 $1,734	(18%)	24 $2,352	(7%)
(2) Motor Neuro-Ophthalmic Disorders	4 $265	(1%)	5 $617	(6%)	9 $882	(2%)
Subtotal	**13** **$883**	**(5%)**	**20** **$2,351**	**(24%)**	**33** **$3,234**	**(9%)**
Total	**67** **$5,330**	**(25%)**	**47** **$5,842**	**(55%)**	**114** **$11,172**	**(33%)**
3. OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA						
a. OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA	3 $261	(1%)	9 $915	(10%)	12 $1,176	(3%)
TOTAL	**268** **$22,070**	**(100%)**	**85** **$12,524**	**(100%)**	**353** **$34,594**	**($100%)**

* Includes R01, R10, R23, P50, K04, and K07 mechanisms.

** Estimated average cost of grants in Strabismus, Amblyopia, and Visual Processing program for FY 1983 is $98,000.

VISUAL PROCESSING AND AMBLYOPIA

VISUAL PROCESSING AND AMBLYOPIA

MORE THAN FOUR percent of the U.S. population have visual impairments due to disorders in the central visual pathways. These disorders, which include amblyopia, loss of depth perception, and other disturbances of binocular vision, are often secondary to strabismus, refractive errors, or abnormalities of the ocular media or adnexal structures. Animal experiments have shown that abnormal visual experience early in life can lead to profound changes in the "wiring pattern" and processing abilities of the visual centers of the brain. If not corrected at a sufficiently early stage, malfunctions of the visual system are usually irreversible. Similar morphological and physiological changes undoubtedly accompany visual experience in human infants. However, better understanding of visual processing and its development should make early intervention possible in order to prevent and cure the disorders. Progress toward this understanding will continue to depend upon the use of a wide range of techniques and a variety of species as model systems.

This section on Visual Processing and Amblyopia consists of three parts: Normal and Abnormal Development, Structure and Function, and Disorders of Visual Processing and Amblyopia. The research objectives of all three subprograms require a multidisciplinary approach and will require studies at the molecular, cellular, behavioral, and integrative levels.

1

NORMAL AND ABNORMAL DEVELOPMENT

INTRODUCTION

WE GAIN KNOWLEDGE of the world through our eyes by neural mechanisms that are laid down very early but that need appropriate interacting environmental influences to reach full potential. Because many defects in visual processing have their origin very early in development, preventing and possibly curing them requires research into the way the visual neural structures grow and differentiate before birth and during infancy.

Research on normal and abnormal visual development encompasses the growth, development, and modification of the visual nervous system including the optic nerve and all visual centers of the brain. The studies include both normal and abnormal processes because abnormalities can best be understood with reference to the normal system; conversely, knowledge of abnormalities can often lead to better understanding of normal processes. The overall objective is to apply new concepts and facts about developmental processes to the prevention or treatment of amblyopia and other visual disorders.

Most of the studies at the molecular level deal with three phenomena: axonal transport, neuronal specificity, and synaptic transmission. Research at the cellular and systems level deals with the differentiation of neurons and glia (including axonal growth and termination, synaptogenesis, axonal sprouting, and regeneration) and neuronal connectivity (particularly the specificity of connections and their alterations under a variety of conditions). Research at the behavioral level involves mainly visual psychophysical studies. The two disease entities most closely associated with this subsection are amblyopia and strabismus; those less directly associated are optic nerve atrophies, myopia, and demyelinating diseases.

SUBPROGRAM OBJECTIVES

- To learn about the normal development of the visual system.
- To elucidate the relative importance of environmental and genetic controls of these events.
- To understand the mechanisms underlying aberrations in development.
- To lay the basic scientific groundwork for an adequate therapy for amblyopia.
- To improve noninvasive methods of evaluating immature visual systems.
- To learn why mammalian optic nerves and tracts in the central nervous system fail to regenerate effectively, preventing restoration of function.

OVERVIEW OF CURRENT RESEARCH SUPPORT

In FY 1981 the NEI funded 82 research grants concerned with normal and abnormal visual development at a total cost of $7,189,000. This represents slightly more than one-half of the research in this area supported in the United States. Other sources of support, in addition to the NEI, include the National Institute of Neurological and Communicative Disorders and Stroke and other Institutes within NIH, the National Institute of Mental

Health, the National Science Foundation, the Veterans Administration, and private foundations.

These grants, whether supported by the NEI or other sources, emphasized research at the cellular and systems level: of the NEI-supported grants, 19 supported molecular research, 51 supported cellular and systems research, and 12 supported behavioral research. Most of the behavioral grants dealt with normal human infants. Most of the grants in cellular and systems research dealt with postnatal development of the visual system and the influence of environmental factors on this process; a few research projects dealt with genetic control and its variation in mutant strains. Most of the other grants in this category supported largely descriptive anatomical studies of the development and function of cells important to the central visual system. The grants for molecular research were diverse.

This level of support is indicative of a very strong research program in Amblyopia and Visual Processing, Normal and Abnormal Development. The large number of granting agencies indicates considerable general interest. Also, the quality of research is very high, occupying a central role in modern developmental biology and neuroscience. Furthermore, the major thrust of the effort, that is, investigation of the effects of visual deprivation, is almost certainly directly related to one form of amblyopia. On the other hand, more research is needed, especially at the molecular and behavioral levels, to increase understanding of the basic mechanisms of normal and abnormal visual development.

RECENT ACCOMPLISHMENTS

Some of the major recent accomplishments in studies of normal and abnormal visual development have been classified according to the type of research and are summarized below.

Behavioral Research

Reliable data on normal visual development in human infants have been obtained only in the last few years. The preferential looking method, used to ascertain whether an infant detects a pattern or a pattern difference (Figure) was first used to assess visual acuity.[1–3] Contrary to traditional opinions, much of a baby's visual acuity develops during the first year of life and approaches normal adult values during the second year. However, stereoscopic acuity seems to have a different time course of development. Stereopsis is present by about 14 weeks, and it undergoes striking development between 15 and 20 weeks.[4,5] Such findings will have considerable impact on therapeutic approaches to strabismus (see Chapter 8, "Strabismus"). Other visual capabilities, including contrast sensitivity[3,6] and color vision,[7] are now being studied by the same methods.

Experiments with animals have demonstrated the existence of a "critical period," in which certain aspects of the ability of the infant visual system to analyze the objective world can be refined and modified by visual experience. The critical period in animal models has been defined in terms of precise anatomical, physiological, and behavioral changes, and approaches developed with animal models are now being applied to characterize the critical period in human infants. Early results indicate that the time course of development for the human infant is quite different from that of animals, as reflected by differences in the onset and duration of the critical period.

FIGURE 1. The preferential looking method for determining whether an infant can detect patterns or pattern differences. When normal infants are shown a plain stimulus and a patterned one, they tend to look at the patterned one, indicating that they can distinguish between the two. (Photograph courtesy of M. V. Dobson.)

Cellular and Systems Research

Studies of Normal Development. The specificity of cortical cells in terms of orientation preference, binocular interaction, and the columnar architecture of the cortex develops to some extent through innate mechanisms,[8,9] but at the same time, normal visual experience is important for full maturation of the visual system.[10,11]

The lamination of the lateral geniculate nucleus and the cortical ocular dominance columns develop from complete overlap before birth to partial overlap at birth. Segregation is completed only after birth, when it is subject to experimental modifica-

tion.[12,13] The development of techniques to manipulate embryonic animals has facilitated this understanding. New insights into development have also been obtained by studies of lower vertebrates, in which the period of cell addition, growth, and differentiation extends into adulthood.[14] Furthermore, lower animals such as amphibia have proved amenable to manipulations that stimulate columnar segregation and permit examination in greater depth of the molecular and cellular bases of development.[15]

The ultimate innervation patterns of mature animals have been found to be more restricted than those seen early in development, as demonstrated by the segregation of individual geniculate afferents from a diffuse arbor into a patchy terminal distribution.[16] Similarly, the postnatal development of interhemispheric connections through the corpus callosum proceeds from initial diffuse connectedness to sharper localization. This development depends to some extent on experience.[17,18]

The technique of three-dimensional reconstruction of nervous tissue from serial electron micrographs has been used to trace the development of optic axons in the crustacean Daphnia. It has provided the most complete description to date of the development, outgrowth, association, and termination of axons. An important discovery from this work is the existence of lead fibers in the outgrowth of axon clusters.[19]

Retinotopic order in the optic nerve has received attention because of its implication in the orderly development of projections in a given pathway. Many species have highly ordered optic nerves but differing axonic ordering in the nerve. Further, there is some suggestion that for certain species the optic nerve may lack order.[20,21]

Studies of Development Through Visual Deprivation. It has been known for nearly 20 years that if kittens are reared with one or both eyes closed during the first few months of life, their visual cortex is changed profoundly.[22] Similar observations were made later in the monkey.[23] Most striking were the effects of monocular deprivation; in this case, the majority of cortical cells, which normally are activated by stimuli delivered to either eye, responded only to stimuli through the exposed eye. Since the responses of many cells in the lateral geniculate nucleus were substantially normal, the fact that the animal was blind in the deprived eye could be ascribed to a cortical defect. In fact, anatomical studies have shown that monocular eye closure leads to abnormal distribution of the geniculate afferents to the cortex.[24]

The defects caused by monocular lid closure can be reversed after eye opening by closing the other eye, but this type of cortical plasticity persists only through the first few months after birth. Furthermore, it has been shown that the ability of a deprived eye to drive cortical cells can be partially restored in approximately 30 percent of the cortical cells by removal of the normal eye. Thus, visual loss after monocular deprivation may be at least partly due to suppression of deprived cortical cells by cells with input from the normal eye.[25] Monocular closure has become a model for deprivation amblyopia which is caused by such defects as congenital cataracts. This model has also helped to resolve the nature/nurture aspects of the developing nervous system.

The effects of monocular deprivation may be largely but not entirely due to a competitive interaction between inputs from the two eyes onto a cortical cell. This hypothesis is based on the observation that abnormalities are less severe in monocularly innervated than in binocularly innervated regions of the cortex.[26] However, interference with normal binocular vision in neonatal monkeys and kittens by producing artificial strabismus causes a marked reduction in the number of cells in the visual cortex that are influenced by both eyes. Further research along these lines might provide a physiological basis for the problem in children with strabismic amblyopia, who often lack the ability to fuse images presented to the eyes and may alternate in their use of either eye.

Studies of the alterations in physiological connectivity that occur in response to various types of deprivation have used several new anatomical methods. Methods developed by workers in the visual system include silver stains,[27] radioautography following axonal transport (for example, transneuronal transport of labeled amino acids),[28] and the ^{14}C-2-deoxyglucose method.[29]

Studies of Development Through Genetic Manipulation. It has been shown that the cortex has a laminated structure and that each layer serves a specialized function. Cortical cells in reeler mutant mice do not occupy their usual laminar position, but nevertheless seem to retain their normal connections and functional properties.[30,31] This mutation provides a useful system for studying cortical organization.

Studies with a variety of hypopigmentation mutants, including human albinos, Siamese cats, and mice revealed an apparent correlation between their lack of melanin production and an abnormal pattern of decussation of their optic nerve fibers. These are the most clear-cut examples of an association between a genetic defect and an abnormality in neuronal connectivity and visual function.[32]

Studies of Development Through Surgical Alteration. Studies of the retinotectal pathway of mammals and lower vertebrates have altered several previous concepts of how neuronal connections are made. The suggestion of a rigid cell-to-cell specificity has been replaced by the idea of a modifiable set

of connections which changes continually in the growing animal and may be induced to change rapidly when the retina or tectum is surgically altered. [33–35]

It is now possible to transplant relatively undifferentiated pieces of mammalian central nervous system tissue into the embryonic cranium, where they mature and make adult-like structures and connections. This technique offers new possibilities for studying neuronal development, the influence of the local cellular environment, and the target and sources of innervation. [36]

Molecular Research

Molecular techniques have only just begun to be applied to developmental studies in visual processing and amblyopia, but work at the cellular and systems level has clearly pointed to the need for an understanding of the subcellular and molecular mechanisms underlying developmental phenomena. As yet, most of the progress in this area has been in formulating techniques for studying molecular mechanisms.

Axonal Transport. While axonal transport has been used at the systems level to trace pathways, some studies have begun on the nature of the molecules transported in normal and deprived pathways to identify substances that may be involved in the establishment and maintenance of connections. [37,38]

Cell Dissociation/Association. Cell surface markers, possibly involved in neuronal connections, have been studied by dissociating cell populations that are interconnected in the adult. Such studies have revealed differential adhesion between cells in topographically similar areas as compared with those in topographically distinct areas. [39,40] This work has been carried out principally in the retinotectal system and has suggested a role for surface markers in the formation of proper neuronal connections in developing systems.

Molecular Profiles. A promising technique for studying the development of the visual system is tissue homogenization followed by two-dimensional gel electrophoresis to produce a profile of protein molecules. Once the population of molecules is thus characterized, changes in the amount of any given protein can be traced during development or plastic reorganization. [41]

Role of Catecholamines. Synaptic plasticity in the geniculostriate pathway of cats appears to be influenced by local levels of catecholamines. [42] This conclusion is based upon the finding that a toxic analog of norepinephrine blocked the shift in cortical ocular dominance that occurs during rearing with monocular lid suture. The effect could be counteracted by microperfusion with norepinephrine. These results suggest that it might be possible to use pharmacological agents, to extend the critical period of development or to confer transient plasticity onto the adult visual cortex.

Role of Nerve Growth Factor. Nerve growth factor has accelerated the regeneration of optic nerve axons in fish and amphibians. [43] This result suggests the possibility of aiding regeneration of mammalian optic axons.

RESEARCH NEEDS AND OPPORTUNITIES

It is difficult to assess impaired vision in babies, and still more difficult to assess the progress of any therapy. Amblyopia becomes less amenable to correction as the child ages; therefore, it is essential that amblyopia be detected early and that therapy be evaluated while the visual system is modifiable.

Research in this area should include at least three approaches. First, the normative data collection already under way should be continued. Second, noninvasive procedures for assessing visual impairment should be developed for use on animals in which surgical or other interventions can also be performed for validation. Third, improved practical techniques and instrumentation for determining visual function in infants should be developed and tested. Finally, the two principal techniques for evaluating visual function in infants, namely, the preferential looking method and the recording of visually evoked potentials, should be directly compared with one another.

Continued research progress on visual development in infants depends upon further development of these and other noninvasive methods. Once infants can be screened for visual defects, then such problems as congenital cataract, albinism, aniridia, astigmatism, strabismus, and ptosis can be studied to determine their deleterious effects and the course of recovery following treatment.

Much needed research on normal development is molecular in nature. It is necessary to learn, for example, the molecular factors involved in the differentiation of cells into nuclei and layers, the migration to their final positions, and the establishment of specific neuronal connections. The hope is that specific cell markers can be identified and used to follow the maturation of cells as they assume their final location and shape. Ultimately, it should be possible to characterize the molecules responsible for determining the fates of cells. Guidelines for developing this knowledge of the visual system will be based on advances in the culture of peripheral

tissues, since investigators have established the existence of diffusible factors responsible for determining the transmitter choice of individual neurons.

Further studies are needed on the mechanism for establishing topographic maps and columnar systems. Some important questions are: What are the roles of cell death and retraction of terminal arbors in achieving the final adult state? What is the interplay between mechanisms of competition, catecholamines, growth factors, visual experience, genetic determination, temporal factors, spatial interaction, and critical period? Some answers can be obtained by studying model systems such as the fish and frog retinotectal projection. The fact that lower vertebrates maintain their plasticity throughout life makes them useful for such studies. Recently, cultured neurons have been introduced for the study of visual processes and development. This advance provides the opportunity to study cells under precisely controlled conditions and lends itself to studies of the development of membrane properties, receptors, and transmitters in individual neurons, and synapse formation between pairs of neurons.

Although most research has focused on the effect of visual deprivation upon the cortical afferent systems and the gross morphological and physiological changes occurring with deprivation, little is known about the specific cellular and ultrastructural changes within the cortex. Methods are now available to identify and label visually deprived cells and to study the morphological differences between normal and deprived cells.

If, as studies of monocular deprivation indicate, competition exists between inputs impinging upon a single cell, then questions arise as to the molecular mechanism underlying this competition and the role of the diffuse, catecholaminergic projection systems in influencing competition. Further, if neurons communicate through trophic factors as well as by neurotransmitters, such factors may be identified by characterizing substances involved in axonal transport.

The effects of visual deprivation can be reversed by experiential compensation (such as suturing the other eye) or pharmacologically (such as applying catecholamines to induce plasticity). Understanding the cellular and molecular mechanisms underlying this reversal will assist the development of clinical approaches for correcting various disorders.

Optic nerve axons degenerate as a result of trauma, demyelination, inflammation, ischemic neuropathy, tumors, and other intracranial problems. Nonmammalian vertebrates regenerate these axons to restore vision, but mammals do not. Many lines of research show that regeneration is more effective in younger than in older animals, but the molecular bases for these regenerative differences are unclear. If mammals are to regenerate optic axons, they apparently would have to lose an acquired factor of maturation or regain a lost mechanism of regeneration. Further studies of regeneration in both young mammals and lower vertebrates are necessary; these should emphasize the early events of embryogenesis, including cell proliferation and death, fate maps, times of cellular specification, morphogenetic cell movements, and axonal outgrowth and termination.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Visual Processing and Amblyopia: Normal and Abnormal Development," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Base

- Investigate the pre- and postnatal development of the visual system at cell and systems levels using animal models.
- Analyze the effects of visual deprivation and abnormal stimulation at (1) cell and systems and (2) behavioral levels.
- Search for factors important for the regeneration of the optic nerve and other components of the visual pathways.
- Study the development of the visual systems of infant humans by developing noninvasive meth-

ods to follow the clinical course of disorders after attempts at medical or surgical interventions.

Program Development Priorities

- Investigate the pre- and postnatal development of the visual system at (1) molecular and (2) behavioral levels using animal models.
- Analyze the effects of visual deprivation and abnormal stimulation at molecular levels.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

VISUAL PROCESSING AND AMBLYOPIA

NORMAL AND ABNORMAL DEVELOPMENT

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Base			
A. Investigate development of the visual system at cell and systems levels using animal models.	25	−3	22
B. Analyze the effects of visual deprivation/abnormal stimulation at 1) cell and systems and 2) behavioral levels.	1) 26 2) 5	−4 1	22 6
C. Search for factors for regeneration of optic nerve and other components of the visual pathways.	9	0	9
D. Study development of visual systems of infant humans by developing noninvasive methods to follow the clinical course of disorders after attempts at medical or surgical intervention.	6	1	7
Program Development Priorities			
A. Investigate development of the visual system at 1) molecular and 2) behavioral levels using animal models.	1) 6 2) 1	4 2	10 3
B. Analyze the effects of visual deprivation/abnormal stimulation at molecular levels.	4	2	6
Subtotal Grants **(% of Program)**	**82** **(30)**	**3** **(4)**	**85** **(24)**
Total Estimated Cost	**$7,189,000**	**$1,141,000**	**$8,330,000**

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2

STRUCTURE AND FUNCTION

INTRODUCTION

THE NERVOUS SYSTEM analyzes the complex visual environment by breaking it down into components contained in the responses of individual neurons, and then synthesizing these signals to provide the substrata for perception. Significant advances have been made in understanding how contrast, contour, brightness, and color are encoded at a cellular level and in determining the underlying neural interactions. To identify these codes, the distinct functions of several visual relays need to be characterized in cellular terms. To understand how the code used by the visual system is produced, the system must be studied by a wide range of molecular, structural, electrophysiological, and pharmacological methods. These studies need to consider the entire visual system up to the highest centers, as well as other structures that may influence its operation. Ultimately, it is important to explore the capabilities of the system at a psychophysical level and to construct theoretical models that clarify the relationship between the system's behavior and its biological substrate. The range of this research, from the molecular to the psychophysical level in a wide range of species, will undoubtedly lead to an understanding of the pathological processes underlying amblyopia and other central visual disorders.

SUBPROGRAM OBJECTIVES

- To understand how visual information is encoded by single neurons or sets of neurons and to define how neurons or neuron sets are interconnected.
- To elucidate the mechanisms by which this encoding occurs at molecular, structural, and electrophysiological levels.
- To analyze the relation between the functional properties of individual neurons or sets of neurons and the visual capabilities of an organism.
- To describe human visual processes in normal and dysfunctional states and to improve specific diagnostic tests.

OVERVIEW OF CURRENT RESEARCH SUPPORT

Of 106 grants totalling $8,570,000 supported by NEI in this subprogram in FY 1981, 68 dealt with neuronal mechanisms at molecular, cellular, or pathway levels and 38 dealt with behavioral aspects. In addition, significant research support related to the concerns of this subprogram is provided by the National Institute of Neurological and Communicative Disorders and Stroke, the Department of Defense, and the National Science Foundation.

Overall, research in the structural and functional aspects of Visual Processing and Amblyopia has remarkable strength. It has attracted some of the finest neurobiologists in the world and has recently benefited from a remarkable array of powerful new methods. These have produced new knowledge about the classically recognized visual pathways,

defined new pathways, and drawn attention to many parts of the visual system that remain to be explored in significant detail. New techniques have allowed the identification of putative neurotransmitters at some sites and have begun to show the extent to which neuronal shape can be related to particular functional properties of nerve cells.

The optimal stimulus patterns for eliciting a response from single neurons at different levels in the visual pathways have been identified. Increased sophistication in creating optimal stimuli in the time, space, and chromaticity domains has accompanied refinements in methods of localizing neurons and recording, storing, and analyzing responses. Results of studies in the alert, behaving animal have the potential to show the relation between the firing of a single cell and a behavioral response.

Research on basic properties of vision has advanced the understanding of stereoscopic depth perception, color vision, pattern recognition, and movement detection. Developments in the physiology of color vision have improved the understanding of the mechanisms underlying acquired color defects associated with eye diseases and cortical deficits categorized as cerebral achromatopsia and color agnosia. Research on "hyperacuities" of visual function has been undertaken to elucidate the relationship between the capabilities of the visual system and the neuronal apparatus.

RECENT ACCOMPLISHMENTS

Behavioral Studies

Historically, behavioral research has been one of the most important approaches to the study of vision; by providing data on the capabilities of the human visual system, it has furnished a baseline against which other approaches, such as electrophysiology, are measured. In addition, it has permitted definition of normal vision and description and measurement of the effects of various diseases on visual performance.

Visual Channels and Hyperacuity. Traditionally, visual acuity testing was the only psychophysical measurement used in the clinic. A few other functions, such as light sense in the peripheral retina, fusion, and stereopsis, were tested only qualitatively. Recent developments in quantitative psychophysical techniques for evaluating visual function are therefore highly significant. The methodology of systems theory was applied to the visual system, first in the space domain by Schade and in the time domain by deLange in the 1950s. Measuring contrast sensitivity for a range of pattern sizes, for example, sinusoidal gratings over a range of spatial frequencies, is now routine. Recently, the roles of image stability and eye movements in these measurements have received attention,[1] and this has been aided by the availability of instrumentation—albeit expensive and delicate—to stabilize targets on the retina.[2]

While there is still some interest in the processing of sinusoidal gratings, studies in the detection of target contrast have turned to the more general question of channeling visual spatial information. Evidence is being produced for the existence of a few size channels accounting for the responses to both sinusoidal patterns and to center/surround stimulation of receptive fields,[3] and attempts are being made to identify their parameters.[4] These findings are being extended from the fovea to the periphery.[5]

The discovery of at least two kinds of retinal ganglion cells differing in their temporal-spatial performance has kindled interest in the determination of similar dichotomies by psychophysical means; these are the so-called sustained and transient mechanisms.[6] While psychophysical techniques have provided the major thrust in studies of normal visual function in humans, such studies are now also being conducted in animals. These are time-consuming and require considerably more technical facilities, but they are valuable in that they allow tests after a variety of interventions. Insofar as animal studies include normal baseline data, macaque responses in visual acuity[7] and reaction time[8] seem to be comparable with those of the human.

Although it has been known for more than a century that finer spatial distinctions can be made than those involved in visual acuity or the minimum angle of resolution, the study of hyperacuity, as it is now called, has only recently been resumed;[9] the data seem to point to complex mechanisms of visual processing. Intermittently exposed stimuli[10,11] open up newer modes of analysis. The subject has sparked interest in developing mathematical models that link psychophysical, anatomical, and physiological observations.[12,13]

Color Vision. Psychophysicists have focused upon the concept that visual information is transmitted separately by chromatic and achromatic channels, which originate in the retina but elaborate more centrally.[14] Especially intriguing are the nonlinear and spatially diffuse yellow-blue signals, which appear to be centrally integrated with those of the red-green luminance pathways.[15] It is clear that the appearance of a restricted area of color is conditioned by the nature of lights distributed throughout the entire visual field.[16] As a result, the color of any area differs markedly from what it would be if it were viewed in isolation.[17]

In a continued attempt to clarify these relationships and their underlying physiology, abnormal color vision is being studied.[18] An explanation of the origin of anomalous trichromatopsia, long a focus of controversy, seems at hand:[19] the idea of clusters of pigments, with its suggested implications for protein structure and genetic coding, is a particular example of the breadth of influences, covering all of biology and psychology, in the research of modern psychophysicists.

Stereopsis. The interaction of signals from the two eyes, forming the basis of fusion, diplopia, and stereopsis, continues to occupy the minds of investigators. For over a decade, random-dot stereograms have been the major tool for testing stereopsis, but more traditional targets, designed to exclude monocular clues,[20] are needed for fine measurement of stereoacuity. Psychophysical techniques are beginning to outline the convergence of pathways from the two eyes, including the summation of signals from the two eyes,[21,22] the transfer of after-effects from one eye to the other,[23] and the long-standing problem of fusion versus diplopia.[24]

Movement. There is accumulating evidence that the visual system processes some features of the retinal image independently of other stimuli. Imaginative manipulation of target presentations in time and space, for example, has demonstrated that detection of "zooming" occurs independently of the detection of side-to-side motion of a target.[25] The perception of motion, as distinct from the perception of position or contrast, is being examined by adaptating paradigms that have been used successfully in other stimulus categories.[26]

Cellular and Systems Research

The nervous system breaks down visual information into subsets that can be identified at the single-cell level. Significant advances have been made in understanding how such factors as contrast, brightness, color, and movement are encoded at the cellular level and in defining the inhibitory interactions, center-surround mechanisms, and others, which produce some of the characteristics of visual processing. Knowledge of the central visual pathways has progressed not only by the demonstration of some of the major organizational features of the classical retino-thalamo-cortical system, but also the elucidation of unexpected complexities of the several extrageniculate pathways. This includes the interrelationships between the several extrageniculate pathways, those between the striate cortex and the extrageniculate pathways, and those between the striate cortex and the extrastriate visual cortical areas.

Much of the progress has depended upon the successful application, and to some extent the improvement, of techniques that use neuronal markers such as ^{3}H amino acids,[27] horseradish peroxidase,[28] or ^{14}C-2-deoxyglucose.[29] In addition, techniques are now available for labeling individual nerve cells with intracellular markers after receptive field properties have been recorded electrophysiologically.[30,31] The synaptic organization of individual neurons can be revealed by extensive serial reconstructions of electron micrographs;[32] individual nerve cells can also be revealed by the classical Golgi method and thereafter sectioned for electron microscopic study.[33–35] These powerful methods, some of which were developed and tested specifically within the central visual pathways, have begun to play a significant role in vision research.

Simple Systems. Cellular mechanisms of visual processing have been successfully studied in a number of selected "simple" nervous systems. The studies have revealed how neuronal integration can occur by means of slow potentials and how a particular type of receptive field property, such as movement detection, is built up and switched into a motor output.[36] Visual systems of flies and vertebrates share common principles of organization.[37] The lamina of the fly's optic lobe, which is roughly comparable to the outer plexiform layer of the vertebrate retina, is a good model for comparing the relative roles of impulse and slow potential transmission. The occurrence of mutations that modify selected components of the visual pathways of insects has been studied, and the discovery of sexual dimorphism in the morphology of particular cell types,[38] related to a dimorphism of mating behavior,[39] has proved of particular interest.

Slow potential integration appears to be a fundamental mechanism of visual processing. Invertebrate nervous systems are useful for investigating this phenomenon because the neurons are generally large, anatomically isolated from other neurons, and often have large processes that permit direct observation of synaptic transmission at dendrites. In the mammalian system, on the other hand, long, slender dendritic processes of cortical cells may preclude direct investigation of integrative mechanisms at the cellular level. In the barnacle visual system, it has been possible to trace through two levels of integration the generation of "off" responses in the absence of regenerative nerve impulses.[40] The serial arrangement and physical separation of cells in the barnacle permit detailed analysis of information processing. Further studies may reveal the microcircuitry and pharmacological basis of the slow potential integration.

Central Optic Pathways. It has become clear that the mammalian visual system does not consist of a single, functionally homogeneous retinofugal fiber group, distributing to a number of separate visual relays. Rather, retinal ganglion cells and their axons

can be classified in terms of several distinct categories that relate receptive field properties to morphological type, axonal conduction velocity, and the central site of axonal termination. Functionally distinct pathways have been reported for a wide range of vertebrate visual systems. Studies of the cat have produced the most detailed classification: three operationally defined, distinct retinofugal systems are recognized and are generally labeled "X," "Y," and "W" pathways.[41–43] The X and Y pathways in the cat are characterized by the nature of spatial summation within the receptive field; that is, linear spatial summation for X cells and nonlinear for Y cells. More precise determination of the response properties of the different cell types has been attempted by systems analysis adapted from communication theory.[44] The precise functional significance of these distinct retinofugal pathways remains to be defined, but it is evident that in many species the sequential analysis of visual information occurs along several distinct and relatively independent retinofugal systems.

In addition to defining a large number of retinotopically and functionally distinct subcortical relays, each receiving its own set of retinal afferents, recent research has shown that there are a number of distinct, separate pathways from the retina to the mammalian cortex. The recognition of a tecto-thalamo-cortical pathway has been important in defining extrageniculate thalamic regions that form a part of the central visual pathways and in indicating one route by which visual messages can reach the striate and extrastriate visual cortex.[45–48] Recent demonstration of a tecto-geniculate pathway[49–51] indicates a close link between the direct retino-geniculocortical pathway and the more indirect retino-tecto-thalamo-cortical path, although the functional nature of this link remains to be explored. Furthermore, it has been shown that the visual system has access to the cortex through a pretecto-thalamo-cortical pathway[52] and that this, too, links by way of a pretecto-geniculate connection[53] to the geniculo-cortical pathway.

The thalamic regions concerned with the tecto-thalamic and pretecto-thalamic connections have been mapped in detail. At least three distinct extrageniculate relays appear to be recognizable in the region of the thalamic nucleus lateralis posterior and pulvinar; each carries a more or less complete map of the visual hemifield, sends fibers to the extrastriate cortex, and receives afferents from the extrastriate (and striate) cortex.[54,55]

Recent studies of the dorsal lateral geniculate nucleus itself have concentrated upon defining the relationships of the functionally distinct X, Y, and W pathways. It has been shown that the pathways are separate within the geniculate relay and that, depending on the species, they are separated to a greater or lesser extent by having their relays within different geniculate layers.[56,57] Morphological studies of the geniculate cells participating in each of these pathways have suggested that each pathway may use a distinct cell type within the geniculate relay.[58,59]

The role of interneurons ("local circuit neurons") within the lateral geniculate nucleus has received much attention but remains largely unresolved. Local synapses in the nucleus are established by intrinsic axons and also by presynaptic dendrites.[60,61] In addition, a significant "local" inhibitory connection is formed by cells in the perigeniculate or reticular nucleus.[62] In their general organization, these cell groups may be characteristic of all thalamic nuclei. The specific role of this small additional circuit and the precise relationship between the reticular and the perigeniculate nucleus need further study.

Studies of the laminar structure of the geniculate relay in many species have demonstrated a striking variety of laminar arrangements.[63,64] The abnormality of the visual pathways associated with pigment deficits (see previous section) also produces a related abnormality of geniculate lamination.[65,66] Such abnormal lamination has been observed in primates, including humans,[67] and may be related to visual disorders and anomalous patterns of visually evoked responses in human albinos.[68] These findings provide a clear example of aberrant central structures associated with visual defects that generally include amblyopia, strabismus, and nystagmus. Studies of the normal human lateral geniculate nucleus have shown a surprising variability in the arrangement of the geniculate laminae, especially for regions receiving afferents from peripheral visual fields, and they have raised questions about the significance of the laminar arrangements.[69]

Studies of retinal terminals within the superior colliculus using modern methods have shown that the uncrossed pathway from the temporal retina is richer than was previously supposed;[70,71] that a pathway, which had been doubted, from the fovea to the colliculus does exist;[72] and that many species have a small crossed component from the temporal retina,[73] whose function remains obscure and at odds with contemporary theories. The relationship between crossed and uncrossed fibers in the mammalian tectum is of interest from a developmental point of view (see Chapter 1, "Normal and Abnormal Development"), but its function is also of interest, showing a compromise between a separation of inputs by layers (as in the geniculate) and a separation by columns or patches (as in the cortex). The colliculus has recently been found to be more than a visual structure, in that representations of the visual, auditory, and somatosensory world exist in different layers within the colliculus, allowing an animal to orient its eyes and head towards a multiplicity of sensory stimuli.[74–76]

Other Subcortical Visual Structures. Many structures exist in the brainstem that deal with functions other than processing of the visual image, such as visual-vestibular interactions, eye movement control, and circadian rhythms. These structures include the accessory optic nuclei, which in the rabbit have cells that respond to very slowly moving stimuli. The nature of their projection to centers controlling eye movements suggest that they play a role in stabilizing the eye in the field of view.[77] The homolog to those nuclei in the bird receives a projection from a specialized population of retinal ganglion cells, the displaced ganglion cells.[78] Other structures include the claustrum, which has an intriguing reciprocal connection with the cortex;[79] suprachiasmatic nucleus, which through connections to the hypothalamus may be important in controlling of diurnal rhythms;[80] ventral lateral geniculate nucleus, thought to be involved with eye movements because of its connections with the cerebellum;[81] and also intralaminar nuclei, the pretectal nuclei, and the parabigeminal nucleus.

Geniculostriate System. The geniculostriate pathway has been studied in terms of its receptive field properties and anatomical organization. In general, receptive field properties of geniculocortical axons resemble those of retinal ganglion cells.[82,83] They can be described in terms of concentric receptive fields, are monocular, and belong to the X, Y, or W pathways.[42,56]

In the cat and many primates, terminal arbors of geniculocortical axons form "ocular dominance columns" within the striate cortex. These columns, which represent alternating stripes of left or right eye innervation, have been demonstrated by electrophysiological methods,[84] fiber staining methods,[85,86] transneuronal transport through the lateral geniculate nucleus of tritiated amino acids,[87] and the selective uptake of ^{14}C-2-deoxyglucose following stimulation of one eye.[88] Individual geniculocortical axons have terminals that spread to more than one column, and further, geniculocortical axons of the X and Y pathways appear to terminate in distinct cortical sublaminae.[31,89] The modifiability of the geniculocortical pathways that can be produced by selective visual deprivation is discussed in Chapter One.

Functional Specialization and Microcircuitry in Cortex. The complex processing of visual stimuli is being further studied within the visual cortex itself. A number of laboratories have studied specific receptive field properties of cortical cells in detail and have established the relationship between the receptive field properties and the laminar position of the cells.[90–94] Geniculocortical axons occur as several distinct systems originating from different geniculate layers and terminating in different cortical layers.[85,89,95] The laminar arrangement of corticofugal systems has been clarified: layers II and III are largely responsible for corticocortical connections, layer V projects to the brainstem, and layer VI sends fibers back to the lateral geniculate nucleus.[96–98] The cells participating in each of these projections have specialized functional properties appropriate for the function of the pathway in which they participate.

Several approaches are being employed to determine the morphological substrate underlying the functional specialization of cortical cells. Cells have been studied by the Golgi technique.[99–102] Cells using particular transmitters can be identified by high-affinity uptake or by immunohistochemistry.[103,104] Intracellular recording and marking techniques have enabled investigators to visualize the full dendritic and axonal arbor of functionally characterized cells and consequently to develop hypotheses on how receptive field features arise from specific intrinsic connections.[31] Opportunities for further study of the synaptic relationships within the cortex are provided by ultrastructural analysis of gold-toned Golgi impregnated cells,[33] cells serially reconstructed from electron micrographs,[32] and the cells marked by intracellular injections. Understanding of the functional significance of cell morphology has been extended through computer reconstructions of the three-dimensional structure of cells.[105]

Many lines of investigation have stressed the columnar organization of the cortex. Well-defined columns (Figure) have been demonstrated in terms of ocular inputs and other receptive field properties, such as orientation selectivity.[106,107] Several corticofugal and corticopetal pathways show a patchy distribution of terminals;[97,108] intracellular staining techniques have further demonstrated that even the intrinsic connections made within a single cortical area by individual neurons spread widely through that area and are patchy in their distribution. All these findings suggest that the cortex consists of functionally discontinuous patches, columns, or modules and that these modules undoubtedly play a major role in the basic function of the cortex. Recent work has also emphasized the possible role of the cortical columns in intracortical inhibitory processes and in the production of specific functional properties of cortical cells.[109,110] Study of the columnar organization of the striate cortex has yielded profound insights into the organization of the cortex in general; the striate cortex will continue as a model for the organization of all cortical areas.

Efferent Pathways. Visual systems in general are characterized by efferent control pathways. They may be efferent pathways that innervate the retina, or they may be efferents that pass from one central relay to an earlier one, as for example, from the visual cortex back to the lateral geniculate nucleus or superior colliculus.[111–114] Efferent fibers from

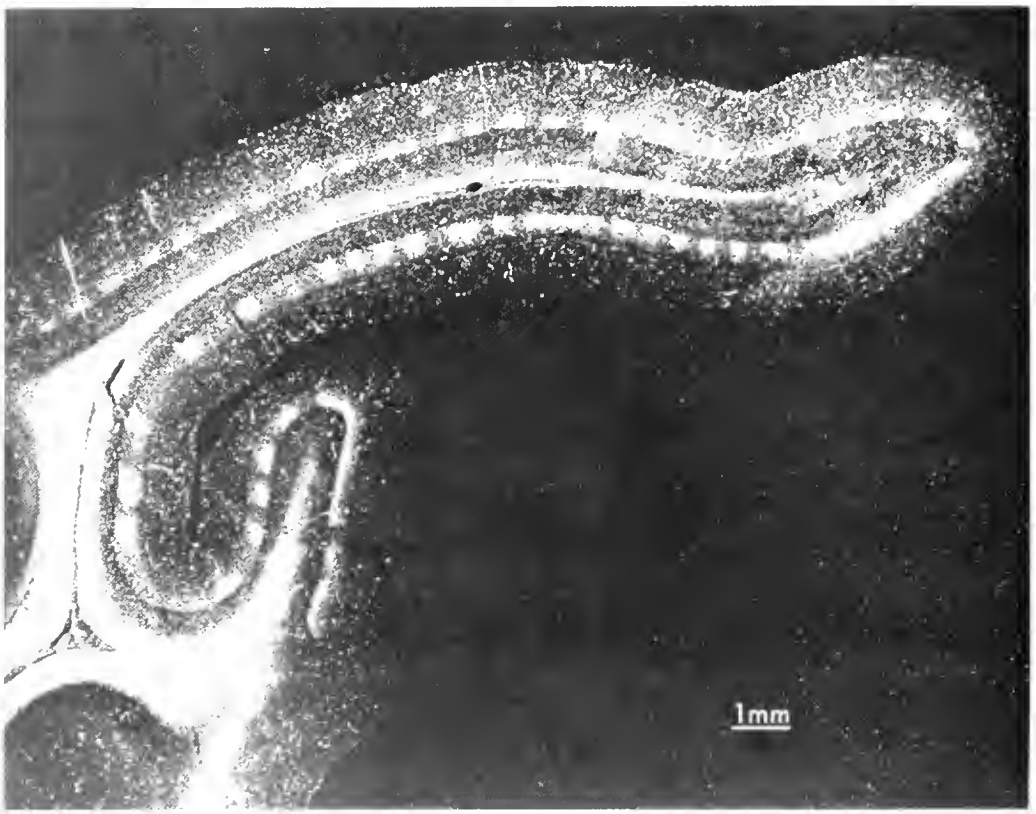

FIGURE 1. Dark-field autoradiographs showing columns in the striate cortex of monkeys who had received an injection of a radioactive fucose-proline mixture into one eye two weeks earlier. (Reprinted from Hubel et al. *Phil Trans R Soc Lond B* 278:377–409, 1977.)

the isthmo-optic nucleus of the bird innervate the retina and appear to control retinal sensitivity by modulating the characteristics of ganglion cell receptive fields.[115] In other species, efferent pathways mediate other significant influences, including the control of retinal structure and circadian rhythms.[116] However, the functional significance of the corticogeniculate system, which may contribute up to 50 percent of the afferent synapses to the dorsal lateral geniculate nucleus, remains obscure.

Multimodal Integration. The interface between the visual system and other sensory systems at a number of central loci strongly indicates that visual processing does not occur in isolation. In the cat and mouse, the organization of multimodal neurons in the deep layers of the superior colliculus corresponds approximately to the general sensory input of the whole body,[74–76] although the receptive fields of the nonvisual input tend to be larger than the visual receptor fields. This overlapping organization of the colliculus appears to contrast with a reptilian tectum in which visual and infrared fields form nonconcentric, spatiotopic maps.[117] The functional significance of nonconcentric maps and disparities in receptive field size are not yet understood, but these observations demonstrate a stage at which visual information may interact with information from other sensory systems to generate the motor outputs for orientation.

Circadian Rhythms. The visual system plays a major role in controlling the endogenous daily rhythms in motor and sensory functions that influence the behavior of all animals. In mammals the suprachiasmatic nucleus receives visual information through the retinohypothalamic tract; in turn it controls daily rhythms, such as melatonin synthesis and locomotion, and integrates the activity of other putative oscillators into a circadian structure.[118–120] The circadian oscillator, which is entrained by the visual system, can also modulate visual function, both in the periphery and central pathways. A circadian clock in the brain modulates visual sensitivity in crayfish[121] and *Limulus*.[122] The daily renewal of photoreceptor membrane is influenced by the central visual system in both the rat[123] and *Limulus*.[116] Annual rhythms are apparent in the ground squirrel visual system, as indicated by the temporary imbalance of retinal metabolism that occurs during and shortly after hibernation.[124] Circadian rhythms in neural activity have been detected in the central visual pathways of the bee,[125] and periodic fluctuations in neural activity

may also occur in the mammalian central visual system.

Extrastriate Cortex. The many extrastriate cortical areas are still being defined and mapped. Accurate maps of the visual field representation have been prepared for a number of them. Each area, like area 17 of the visual cortex, has an orderly map of all or most of the contralateral hemifield, and each has a distinct architectonic structure and a distinct set of afferent and efferent pathways.[126–128] Each of the extrastriate cortical areas may have distinct functions; for example, certain areas may specialize in depth, color, or directionality of movement.[129–131]

Physiological Basis of Visual Functions. Physiological studies have attempted to determine the mechanisms underlying such visual functions as stereopsis, color vision, acuity, spatial relationships, and pattern recognition.

Several investigations in various cortical areas in the cat, sheep, and monkey have provided clues to the cellular mechanism of stereopsis. These studies have shown that cortical cells tend to be of three types, responding optimally to objects in front of, on, or behind the plane of fixation.[129,132–136] Specific cell types may also respond to movement in depth, that is toward and away from the observer, by being sensitive to different directions of movement by the two eyes.[54,55]

Color mechanisms have been investigated in structures ranging from the retina, to geniculate, to striate cortex, to extrastriate cortex. In the retina and lateral geniculate nucleus, color opponent cells are responsible for analyzing the chromatic aspects of the visual stimulus.[137–139] The selectivity for colored stimuli is maintained for the oriented striate cortical receptive fields, and a functional segregation of color-sensitive cells has been suggested.[140,141] A more sophisticated study of an area in the extrastriate cortex known as V4 has revealed cells with greater variety of peak color sensitivity than previously observed, as well as more global features of the distribution of colors in the visual field.[142,143] This last feature may be the cellular mechanism for alterations of perceived color caused by the presence of different colored objects in the visual world, as described by Land.[144]

While there is a good correlation between receptive field measurements and two-point acuity, the physiological basis of vernier acuity is elusive. There have been speculations, however, that relate vernier acuity to cortical anatomy and receptive field features.[32,33]

The output of the extrastriate visual areas appears to be channeled in two principal directions: the parietal cortex and the inferotemporal cortex.[145,146] Research has indicated the role of the parietal cortex in visual attention and in goal-directed movements.[147] The cells in this area have visual sensory fields, and their activity is enhanced when the stimulus is to be the target of a movement. They can also serve more than one modality, having somatosensory as well as visual receptive fields.[148] Research has also begun to probe the role of the inferotemporal cortex in pattern discrimination.[149,150] Both of these research areas have important implications for diagnosing and treating patients with cortical lesions.

Molecular Research

Neurotransmitters. The identification of neurotransmitters was one of the recommended priorities of the previous national vision research Plan. Although progress has been modest, it has been significant. In particular, significant gains have been made in developing techniques for identifying transmitters in the central nervous system. These include examining the release of endogenous compounds from tissue slice preparations, uptake of radioactively labeled transmitters or transmitter precursors followed by autoradiography, synthesis of transmitters from radioactive precursors, receptor binding by the appropriate ligands, electrophysiological studies using iontophoretic application of transmitter candidates, immunohistochemical procedures to visualize the localization of transmitters or of their synthetic enzymes, and specific retrograde transport of transmitters by the cells that use them.

The transmitter that perhaps has been most clearly established to exist in the visual cortex is gamma-amino butyric acid (GABA). This has been established by uptake studies[103,151] and by immunohistochemical localization of the GABA synthetic enzyme glutamic acid decarboxylase.[152] Evidence from these studies suggests that GABA is employed by a specific population of cells, the smooth stellate cells, which are thought to be responsible for mediating inhibition in the cortex. An inhibitory role of GABA is also suggested by the changes in the physiological properties of visual cortical cells induced by the iontophoresis of an antagonist to GABA, bicuculline.[153] These experiments suggests that local inhibitory mechanisms are important in producing receptive field properties, such as directionality and orientation specificity. Both release and localization studies have suggested that aspartate and glutamate may be involved in the visual pathways, specifically those responsible for the recurrent pathway from cortex to geniculate.[154]

Modulators of Synaptic Action. In recent years, studies have demonstrated that molecules released from nerve terminals can play longlasting neuromodulatory roles. A compound similar to LHRH (luteinizing hormone releasing hormone), when released from a nerve terminal in the frog superior

cervical ganglion, for example, can cause postsynaptic voltage changes in many ganglion cells lasting several minutes.[155] Biogenic amines also are involved often in such neuromodulatory roles. Iontophoresis of norepinephrine, for example, markedly facilitates evoked responses of the lateral geniculate nucleus, mimicking the effects of locus coeruleus stimulation and acting by way of alpha-adrenergic receptors.[156] The possible role of catecholamines in cortical plasticity is discussed in Chapter 1.

The discovery of an abundance of gut peptides and their receptors in mammalian brain is one of the more thought-provoking observations of the past decade. It now seems likely that long-term modulatory signals, evoked by released peptides, could be as significant in central information processing as the extensively studied quantal events. The presence of these substances in various brain areas has been demonstrated primarily by immunochemical techniques, including radioimmunoassay and immunohistochemistry. The release of polypeptides from slice preparations has been studied in the hypothalamus but not yet in the cortex. The most prevalent polypeptide identified in the cortex is cholecystokinin.[157-160] Vasoactive intestinal polypeptide (VIP) is also commonly found in the cortex.[161-163] Both of these polypeptides appear to be in small neurons, possibly smooth stellate cells. Other neuropeptides such as neurotensin[164,165] and somatostatin have also been found in the cortex.[166,167]

Other polypeptides not likely to be found in the visual cortex are: substance P, which is found only in frontal cortex,[168,169] and enkephalin, corticotropins, biombesin, and carnosine, which have not been found in any cortical area.[170] The most extensive work on the localization of peptides in the visual system has been done for the retina, in which a number of classes of amacrine cells each contain a unique peptide transmitter.[171,172]

Interest in neurotransmitters and neuromodulators has increased for both experimental and therapeutic reasons. Identifying them and their antagonists greatly facilitates the study of the functional significance of various pathways and structures in the visual system. The practical value of these studies lies in the possibility of developing pharmacological agents for use in treatment. The classic success story of this approach is, of course, the treatment of Parkinsonism. The discovery of the autoimmune nature of myasthenia gravis resulted directly from the identification and isolation of the acetylcholine receptor. The possibility of restoring plasticity to the adult visual cortex has been mentioned in Chapter 1.

Markers of Cell Function and of Developmental History. Until recently, neurons and glia could be identified only by their morphology. Now, the morphological characteristics of functionally-described cells can be described in a few cases. Complementing this approach is the correlation of cell morphology with biochemical markers. Through endogenous fluorescence, high-affinity uptake, or immunofluorescence, it is possible to classify cells sharing molecular specificities. Neurons can be distinguished from glia either by tetanus toxin binding or by antibody binding to galactocerebroside or glial fibrillary acidic protein.[173] Antibodies also are available that bind to transmitter-releasing nerve terminals but not to resting ones.[174] Monoclonal antibodies to receptor cells in the retina have been described.[175] Experiments with monoclonal antibodies have demonstrated a dorsal-ventral gradient in avian retina, in agreement with a previous suggestion by Roth and Marchese and by Gottlieb; an antigen has been identified that is over thirty-fold enriched in the most ventral as compared to the most dorsal part.[176] These very recent technical innovations have not yet been directly applied to the central nervous system.

Axonal Transport. One advantage of the visual system for the neurobiologist is the ease with which axonal transport can be studied. Most of the data on the routes of transport—fast, intermediate, and slow—and the types of protein associated with all three have been acquired using the retinofugal pathways.[177] Similarly, the most extensive information on transneuronal transfer is from visual pathway studies.

Axonal transport has been similarly useful to the visual scientist. Anterograde and retrograde transport, as well as trans-synaptic transfer, have been widely used by the neuroanatomist to map the major connections of the visual system.

The proteins of the axon and the nerve terminals must be synthesized in the cell bodies and transported intra-axonally. By identifying transported proteins on one- and two-dimensional gels, proteins specific to the visual system and proteins present in terminals of the lateral geniculate nucleus, but not of the superior colliculus, have been identified.[178,179] Proteins involved in axonal regeneration might also be identified.[180] It may be possible to use these procedures to identify protein alterations in terminals undergoing plastic or developmental changes.

RESEARCH NEEDS AND OPPORTUNITIES

Behavioral Research

Future behavioral research will provide a basis for understanding the physiology and anatomy of the visual system and for devising new diagnostic tools and methods to treat visual disorders.

Important insights have been produced by mathematical models of visual function. These models rely upon a detailed description of the psychophysical abilities of the visual system, along with the anatomy and electrophysiological properties of single cells, and they provide a means of relating the two kinds of descriptions of the system. Attempts should be made to correlate a cell's ability to discriminate stimuli with the animal's ability to respond. Ideas about how the nervous system operates may require models that remap the stimulus domain (for example, object space or color space) by mathematical concepts such as group theory, non-Euclidian geometry, Fourier transformation, and processing by nonlinear operators. Understanding the nervous system may require visualizing the activity of groups of neurons as well as single cells. Global approaches to perception and cognition have traditionally used vision as their point of departure: Gestalt psychology as practiced in the first third of this century, the Retinex description of seeing colors proposed by Land, and random dot stereograms. These are all attempts at ordering visual experience with concepts that transcend simple psychophysics. This approach ultimately will be significant in understanding perceptual abnormalities.

A major focus of psychophysical research that hints at the existence of certain neuronal mechanisms is the idea of the channel. For example, a given narrow band of spatial frequencies may be processed independently of other spatial frequencies; and changing size may be processed independently of sideways motion, contrast, and intensity changes. There may be channels also for other processes such as color, orientation, and flicker.

Psychophysical techniques are widely used for diagnosis. Further refinements in these techniques will facilitate clinical investigations into the etiology of amblyopia. If a particular channel corresponds to a neural mechanism, and if this mechanism is vulnerable to a disease, then a psychophysical test of the channel might aid differential diagnosis. Furthermore, if the mechanism (for example, a type of neuron) has a known location, then a psychophysical test could pinpoint the site of pathology.

Psychophysical methods that require cooperation cannot be used with infants, or some adults. Instead, evoked potential methods might be developed to permit use of the channel tests with infant patients and to provide supplementary objective evidence when a psychogenic visual disorder is suspected in adult patients.

Instead of analyzing the waveform of the evoked potential, the electrical signal at the scalp can be regarded merely as an indication that the visual signal has arrived: the evoked potential can be regarded as an objective equivalent of the "yes/no" responses of the psychophysical subject. Just as in psychophysics, the burden of effort lies in manipulating the stimulus to "dissect" the visual system. Perhaps the major scientific problem is to determine which evoked potential procedures correlate with psychophysics. The major technical problem is to devise methods that are sufficiently fast and undemanding to be used with infants.

Cellular and Integrative Research

A number of research areas should be continued but pursued at higher levels of resolution; for example, using microcircuitry instead of tracing long tracts, incorporating new methods such as intracellular marking techniques, cross-correlation, and preparation of tissue slices. In addition, attempts should be made to relate insights obtained at the cellular level to an understanding of the functioning of the whole system.

A number of physiological and anatomical channels have been identified in the pathway from retina to cortex. Further research is needed to clarify the relationship of the channels to one another and the precise contribution of each to a common recipient structure. These channels include individual cell types, such as the X, Y, and W types of ganglion and geniculate cell, and entire nuclei, such as the thalamic nuclei that relay information from the retina to the cortex, including the geniculate, pulvinar, lateroposterior nucleus, and medial interlaminar nucleus.

The function of a number of substantial pathways in the visual system remains a mystery. Undoubtedly, it will be necessary to know the role of each in visual processing in order to understand the function of the whole system. These pathways include the recurrent projection from cortex to geniculate, the loop from cortex to claustrum and back, the corticotectal pathway, and others.

Within the cortex, further studies are needed of the functional cell classes and the contribution of each to form vision, eye movement, and other visual functions. However, it will not be sufficient simply to reclassify cells or reestablish the same classification systems in additional species, without contributing new and heuristically useful concepts of cell function.

A major focus of research in the next five years and beyond will be to elaborate the details of the cortical circuit. Information is needed on the contribution of each cell type to the functional properties of other cells, the inter-relationships of various columnar systems, and the relationship between the local intracortical connections and the inputs from other cortical areas. The research should be conducted at the ultrastructural level as well as the level of the light microscope, to obtain a complete description of the circuitry, similar to that produced

for the retina. Advancement in this area will be assisted by the recent development of numerous anatomical and electrophysiological techniques.

New evidence suggests that the cortical column is more ubiquitous than had been previously suspected. It appears to exist not only in every cortical area, covering all modalities, but to be used in a number of ways, including segregation of afferents, grouping together of cells sharing certain functional properties, corticocortical connections, local inhibitory mechanisms, and metabolic activity. Some of these aspects of cortical organization have been demonstrated by new techniques, which will be employed to elucidate further the nature and relationship of the different columnar systems.

A clear priority for vision research is to attempt to understand the role of multiple cortical areas in visual function. Over the next few years investigators should complete the mapping of these areas, and then their emphasis can shift toward describing the cells' response properties and the functional architecture of each area. It has been suggested that the purpose of so many areas is to break down the visual world into its characteristic features (for example, color, movement, depth). Eventually, it will be necessary to address the question of how this segregation of neuronal activity is reunified into a single percept.

Attempts should continue to determine the function of higher cortical areas, and to develop new techniques and new theoretical insights for this purpose. Some inroads have been made in this area by doing recordings in awake, behaving animals. Such studies will help to establish a correlation between the properties of single cells and the behavior of the whole animal.

Much of this research has been conducted in primates and other mammals, but similar studies in lower vertebrate species and invertebrates have and will continue to provide clues to further studies in higher species. It is often easier to demonstrate a direct link between anatomical and physiological findings and the behavior of animals in simple systems. For example, the study of bird song,[181] has had far-reaching implications for understanding the language, the role of hormones and experience in development, and the existence and nature of sexual dimorphism of brain function.

Numerous anatomical and physiological techniques have been developed, the further application and refinement of which will provide extraordinary opportunities for advances. Perhaps most striking are the anatomical techniques, including tracing neuronal pathways in the anterograde direction with radio-labeled amino acids and in the retrograde direction with horseradish peroxidase, transynaptic transport to demonstrate secondary connections, double labeling with various fluorescent dyes, labeling of active neurons with 2-deoxyglucose, and three-dimensional computer graphic reconstructions. Among the physiological techniques are cross-correlation analysis, tissue slice preparations, and intracellular marking of functionally identified neurons. Future advances are expected to emerge from the highly complex techniques of positron emission tomography and related extracorporeal methods for visualizing brain activity. These are particularly promising because they are noninvasive and therefore applicable to studies of normal human vision as well as diagnosis of visual disorders.

Research on Molecular Basis of Neuronal Interaction

Studies should be continued to identify the transmitters used at various levels in the visual pathway. To date, only a small percentage of neurons have been associated with specific transmitters. As transmitters are identified, it will be necessary to develop appropriate antagonists for use in pharmacological studies. This research is expected to establish the function of each element of the visual pathway and provide a basis for therapeutic procedures.

Research should continue along two lines: localizing previously identified transmitters in the visual system, including peptides, and identifying new transmitters. The techniques that will be useful for these studies include immunofluorescence and radioimmune assay, high pressure liquid chromatography and gas chromatography/mass spectroscopy, preparation of tissue slices and culture of single dissociated cells, iontophoresis with electrophysiology, specific receptor probes (such as bungarotoxin for the acetylcholine receptor), and uptake and kinetic studies.

The use of monoclonal antibodies will revolutionize molecular studies of the nervous system. For example, they can be used in neurotransmitter studies. They can also be used to distinguish subpopulations of neurons if these neurons differ in their surface antigens or to study the distribution of antigens on the neuronal surface. There is cause for hope that more such studies can now be done in the visual system; for example, investigators have elicited specific antibodies to retinal photoreceptors[175] and to different neuronal types in the nerve cord of the leech.[182] Specific antibodies can also be used as inhibitors or cytotoxic agents. Antibodies to surface antigens can, in the presence of complement, cause selective cell lysis and in this way eliminate specific cell types from the overall population.

Axonal transport will also be used as a tool for differentiating between various classes of neurons and identifying transmitters and trophic substances. The availability of immune precipitation techniques should greatly facilitate such studies. The nature of the material involved in transneuronal transfer also

merits investigation. Finally, the involvement of transport processes in development needs to be explored.

Dissociated cells in tissue culture will provide an excellent preparation for studying many phenomena at the molecular level. With this technique, investigators can study the presence of receptors and membrane channels, their development, and their interaction with monoclonal antibody preparations.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Structure and Function," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Base

- Investigate the functional specialization of cells in the visual pathways and relate their function to their structure and connectivity.
- Elucidate the role of the multiple afferent pathways and the efferent pathways in the processing of visual information.
- Map and analyze the large number of extrastriate cortical areas having visual representation and relate single cell activity to behavioral responses in alert primates.
- Evaluate the "channel hypothesis" of human visual processing and its implications for the diagnosis and management of visual disorders.
- Relate psychophysical data in humans with behavioral and physiological findings in animals and study human psychophysics as a guide to physiological studies.
- Delineate human visual processes in normal and dysfunctional states.
- Develop psychophysical and objective methods for studying human visual processes in normal and dysfunctional states.

Program Development Priorities

- Identify neurotransmitters, peptides, and other chemicals important in the signaling between cells in the visual pathways.
- Identify molecules involved with cell specificity and function.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

VISUAL PROCESSING AND AMBLYOPIA

STRUCTURE AND FUNCTION

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Base			
A. Investigate cells in the visual pathways: functional specialization and its relationship to structure and connectivity.	25	−2	23
B. Elucidate the role of afferent and efferent pathways in processing visual information.	19	−1	18
C. Map and analyze extrastriate cortical areas; relate single cell activity with behavioral responses.	8	3	11
D. Evaluate the "channel hypothesis" of human visual processing.	11	−2	9
E. Relate behavioral/physiological studies in animals to human psychophysical data; study human psychophysics as a guide to physiological studies.	10	−1	9
F. Delineate human visual processes in normal/dysfunctional states.	12	−1	11
G. Develop psychophysical and objective methods for studying human visual processes in normal/dysfunctional states.	15	−3	12
Program Development Priorities			
A. Identify neurotransmitters, peptides, other chemicals important in signaling between cells in the visual pathways.	3	6	9
B. Identify molecules involved with cell specificity and function.	3	5	8
Subtotal Grants	**106**	**4**	**110**
(% of Program)	**(40)**	**(5)**	**(31)**
Total Estimated Cost	**$8,570,000**	**$2,210,000**	**$10,780,000**

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3

AMBLYOPIA

INTRODUCTION

DISORDERS OF VISUAL processing are among the most frequent causes of visual disability. Among these disorders are amblyopia and disturbances of binocular vision, including sensory adaptation to misalignment of the visual axes and impairment of stereoscopic depth perception. Amblyopia is actually a group of conditions having different etiologies and clinical characteristics. In all cases, vision is reduced despite optimal refractive correction and the absence of detectable structural lesions in the visual system. Amblyopia may be unilateral or bilateral. It occurs in 2 to 4 percent of the population and is the most important cause of visual impairment in children. Although amblyopia itself seldom causes total blindness, the better eye of amblyopes may be more susceptible to loss through injury. [1]

Unilateral amblyopia is caused by strabismus in about 50 percent of patients, and by anisometropia in a somewhat smaller percentage. Abnormalities of the ocular media or adnexal structures may produce visual deprivation in early life. [2] These abnormalities may be either unilateral or bilateral and may preclude the sharp focusing of images on the retina and thereby cause total or partial pattern vision deprivation during a critical period of development. In most instances of unilateral amblyopia, abnormal binocular interaction also occurs: the dominant eye actively interferes with and inhibits the ability of the amblyopic eye to transmit information to the higher visual centers.

Amblyopia may involve selective reduction in sensitivity to certain types of visual stimuli; for example, sinusoidal gratings with particular spatial orientations, (as occurs in meridional amblyopia, associated with astigmatic refractive errors) or frequencies, or situations in which test letters are surrounded by other forms instead of being viewed in isolation (the "crowding phenomenon"). Motor abnormalities (eccentric or unsteady fixation) are seen in some but not all amblyopes, as are abnormalities of the pupillary light reaction. Vision in amblyopic eyes may be only slightly impaired or so impaired as to produce almost total inability to discriminate forms. Severe amblyopia may represent a distinct disorder. In some cases, even markedly reduced vision can be rapidly restored to normal by simple occlusion therapy (patching the dominant eye), while in others prolonged treatment fails to improve even moderately reduced vision. Treatment sometimes produces stable and permanent improvement, but at other times prompt regression occurs.

These distinctions imply that amblyopia exists in many forms, which overlap in as yet unpredictable ways. Throughout this section the term amblyopia is used to refer to all forms collectively, but a major thrust of research on this disorder is better delineation of these forms with particular regard to the prognosis for successful treatment.

Disorders of binocular visual processing generally are associated with strabismus. They have received much less attention than amblyopia, particularly in animal investigations, although they are nearly as common and are important to the understanding of strabismus and the ability to treat it. They are considered in Chapter 2, "Structure and Function," as well as here.

Because disorders of visual processing appear in large part to be acquired and environmentally determined, they are in principle preventable or curable if treated early. In recent years, studies of experimental visual deprivation in animals and psychophysical and electrophysiological studies in humans have contributed enormously to the understanding of these conditions. Advances in surgical and anesthetic techniques have greatly improved the ability to remove anatomical barriers to visual development early in life. Nevertheless, these disor-

ders remain a major challenge in both clinical and public health settings.

SUBPROGRAM OBJECTIVES

- To understand the basic mechanisms of amblyopia through (1) elucidation of physiological alterations, (2) better characterization of the visual deficit in humans, and (3) investigation in appropriate animal models of functional abnormalities that are known to occur in human amblyopes.
- To determine the natural history of amblyopia and to be able to predict treatment outcome from factors such as varying degrees of sensory impairment, age of the patient, and duration of the disorder.
- To develop and evaluate simple, reliable means of measuring monocular and binocular visual function in infants and young children to diagnose or detect potential sensory disorders at an early age.
- To develop new treatments for amblyopia and other sensory disorders that (1) are effective in older children and adults, and (2) do not risk creating a visual deficit in the uninvolved eye or interfering with the development of normal binocularity.

OVERVIEW OF CURRENT RESEARCH SUPPORT

NEI provides most of the support for research in amblyopia. In FY 1981 this support consisted of a total of nine grants totalling $646,000; two of these grants are for the development of techniques for the large-scale screening of very young children for visual disorders; six grants support research to characterize better the various types of amblyopia; and one grant supports research to develop improved tests of visual function in amblyopia and other sensory disorders.

RECENT ACCOMPLISHMENTS

Human Psychophysical and Electrophysiological Studies

It is well recognized that visual defects in amblyopia are complex and not adequately defined by visual acuity alone. Recent psychophysical studies have attempted to clarify the nature of these defects by determining the contrast sensitivity function for sinusoidal gratings in adult human amblyopes. Groups of amblyopes have been found with reduced contrast sensitivity at both high and low spatial frequencies, at high frequencies only, and with normal sensitivity at all frequencies but with subjective distortion of suprathreshold gratings.[3] This distortion has long been recognized clinically and is confirmed by other recent psychophysical studies.[4] Abnormal increment threshold spectral sensitivity curves, indicative of a subtle defect in retinal color vision processing, have also been observed.[5] Furthermore, minor abnormalities of visual function have recently been detected in the dominant eye of amblyopic individuals.[6]

Electrophysiological studies in amblyopia have yielded somewhat inconsistent and confusing results. It is now generally agreed that in amblyopia the visually evoked potential (VEP) is reduced in amplitude, at least when fine patterned stimuli are employed. Retinal abnormalities in human amblyopia are being explored by psychophysical and electrophysiological studies. Abnormal electroretinographic (ERG) responses to patterned stimuli have been observed recently in amblyopes,[7] but normal responses have been reported for focal ERGs recorded from the amblyopic fovea.[8]

There has been considerable interest recently in the use of the patterned stimulus visually evoked potential and techniques based on grating resolution to measure visual acuity in infants and the effect of amblyopia therapy. Occlusion therapy can alter the visually evoked potential in both the occluded and the amblyopic eye.[9] One group of investigators[10,11] used patterned stimulus visually evoked potentials during amblyopia treatment of very young infants and children after removal of congenital cataracts or other ocular obstructions. Patching regimens were adjusted to maintain approximately equal visually evoked potentials in the two eyes.

The forced choice preferential looking system, which employs gratings of different spatial frequency, has also been used to monitor the course of amblyopia therapy in a small number of esotropic infants.[12] This method is not generally applicable to children over one year of age, but the addition of

reinforcement techniques may make it useful in older children. [13]

Animal Studies

The consistency of results from experiments using different animal species, including primates, and different forms of visual deprivation that closely simulate common human amblyopiogenic factors have strengthened the view that the animal visual deprivation syndrome is a valid model of human amblyopia. Studies with animals are further defining the period of susceptibility to monocular deprivation from occlusion and media opacities and are contributing to our basic understanding of amblyopia.

The physiologic abnormalities that have been observed in the lateral geniculate nuclei and the retinal ganglion cells of cats subjected to various kinds of abnormal visual experience are providing a means for studying the contributions of vision deprivation and abnormal binocular interaction in the development of amblyopia. Investigation of the effects of postcritical period enucleation and pharmacologic manipulations has renewed interest in the hypothesis that active neural inhibition contributes to amblyopia at the cortical level. Furthermore, the lateral geniculate and cortical components of the deprivation syndrome are now recognized to be independent to some degree, and different cell populations in the lateral geniculate nucleus (X cells and Y cells) may be sensitive to different types of deprivation. These findings suggest a possible basis for the heterogeneity of human amblyopes, although precise parallels are not apparent at present.

Clinical Studies

Since the concept of a critical period in visual development emerged from animal experiments, clinical investigators have attempted to determine the limits of the period during which visual deprivation may cause amblyopia, and the severity and treatability of the resulting amblyopia at different stages of development.

Recent clinical studies have roughly delineated the period of susceptibility in humans to the effect of short- or long-term severe monocular visual deprivation. [14] It has been reported that infants with monocular congenital cataract achieved good visual function if their cataracts were removed during the first six weeks of life, followed by immediate optical correction and patching regimens. [11] A retrospective analysis of visual outcome in children with congenital and traumatic cataracts has demonstrated that deprivation amblyopia may develop as late as age ten, [15] and recent studies in Japan have shown that up until the age of 18 months, one week of occlusion may cause amblyopia that is sometimes unresponsive to treatment. [16] In both instances, there has been a large amount of unexplained individual variation.

Unfortunately, this extensive and unexplained variation within groups of apparently comparable individuals precludes the use of these results to make accurate predictions for individuals. Furthermore, the beginning of the critical period is uncertain and there is still too little reported experience with prompt and vigorous treatment of early or congenital deprivation to know which conditions, if any, can be reversed. Variations in contrast sensitivity function and electrophysiological test results among amblyopes suggest a possible basis for predicting the outcome of treatment, but no such correlations have yet emerged.

Diagnosis and Detection of Amblyopia

The problem of detecting amblyopes and potential amblyopes at an early age has been addressed in a number of studies. Screening for refractive errors at one year of age has been advocated on the basis of a strong correlation between significant hyperopia, astigmatism, or anisometropia at this age and the future development of strabismus or amblyopia. [17] Noncycloplegic retinoscopy has been used to detect significant refractive errors in children age one to two and one-half in a large-scale screening program in Israel. [18] The development of a new simple test has revived interest in the use of stereopsis testing for screening. [19]

Both visually evoked potential and forced preferential looking systems are promising means of diagnosing amblyopia in infants and following the course of therapy. Both, however, are cumbersome, may fail to detect some amblyopes with normal contrast sensitivity functions, and are difficult to employ in the age range of one to three and one-half years, when a majority of cases of "straight-eyed" amblyopia appear. Detection of significant refractive errors may be the key to early identification of the actual or potential amblyope. Appropriately designed tests of stereopsis do show promise for use in screening. [20] However, the feasibility and usefulness of doing this in large-scale screening in this country remain to be determined.

Treatment Modalities

Occlusion of the dominant eye remains the mainstay of amblyopia treatment, but alternatives continue to emerge. The use of cycloplegia combined with manipulation of the refractive correction (penalization) has become popular, particularly in Europe. Its usefulness has been limited to relatively mild amblyopia. It also is capable of producing amblyopia in

the atropinized eye.[21] Intense interest was generated by reports that short periods of occlusion using rotating striped discs (Cambridge Visual Stimulator CAM technique) could dramatically improve amblyopic vision.[22] However, subsequent investigations, including a multicenter study organized by the American Association for Pediatric Ophthalmology and Strabismus, have failed to prove the usefulness of this technique.[23]

Animal studies have indicated that anatomic and pharmacologic modification of the nervous system may permit reversal of at least some of the effects of visual deprivation in the mature animal.[24–26] Although the specific techniques employed in animals are unlikely to be directly applicable to humans, the results of these studies suggest that more successful therapy than conventional occlusion for older children and adults may be developed.

RESEARCH NEEDS AND OPPORTUNITIES

Basic Research

The techniques for studying visual deprivation and amblyopia in animals should continue to be refined so that results are more relevant to human conditions. Emphasis should be placed on techniques that result in less severely reduced acuity and preserve some degree of binocularity. The use of simultaneously presented binocular stimuli should be explored with such models to find animal analogs of the well known clinical phenomena of suppression, anomalous retinal correspondence, and monofixation.

Efforts to characterize the amblyopic visual defect should be continued. Methods of quantifying overall distortion for evaluation of the animal and human visual systems need to be devised. Retinal involvement in human amblyopia and the animal visual deprivation syndrome needs to be clarified. Psychophysical or electrophysiological techniques for isolating independent cortical and retinal contributions to amblyopia would be of great value. Human analogs of X and Y cell dysfunction should be sought. An active effort is needed to obtain specimens for studying the histopathology of the human lateral geniculate nucleus in amblyopia.

Clinical Research

Additional data on the effects of ocular media opacities at different ages are needed to refine predictive capabilities. In particular, we need to know at what age the critical period in visual development begins and by what age congenital unilateral media opacities must be corrected in order to prevent profound, irreversible amblyopia. The natural history of ametropic and anisometropic amblyopia should be investigated in large-scale prospective studies to determine the optimal age for screening for refractive errors and for instituting treatment to prevent amblyopia. Improved means of determining if severe irreversible amblyopia has developed are urgently needed so that unnecessary surgery to correct organic ocular abnormalities may be avoided.

Other equally important future investigations should include a study of the sensitivity of the infantile visual system to strabismus. For instance, the critical period during which misalignment of the visual axes causes a permanent defect of binocular vision needs to be determined. This information is badly needed for use in determining the urgency for correcting eyes by optical or surgical means to restore fully normal binocular function.

Other sensory anomalies associated with strabismus, such as suppression and anomalous retinal correspondence, have received less attention from clinical investigators in recent years. More future emphasis is needed on these anomalies through psychophysical, electrophysiological, and clinical studies, including the use of the phase difference haploscope. Through these studies much can be learned about the nature of central inhibition and its effect on various aspects of the visual pathways.

Research on Diagnosis and Detection

Methods are badly needed for reliably and simply measuring visual acuity in children one to three and one-half years old, in whom amblyopia is difficult to diagnose and relatively easy to treat. Large-scale screening programs to detect amblyopic and potentially amblyopic children at an early age represent probably the most effective means of reducing visual morbidity from this condition. Pilot programs should be conducted to determine the best approaches to such screening.

Treatment Research

Multicenter studies such as the ad hoc study that evaluated the CAM stimulator are highly worthy of support. It would be desirable to maintain a network of centers to evaluate new treatment techniques. In the laboratory, emphasis should be placed on further evaluation of the ability of dominant eye occlusion at different times to reverse the effects of visual deprivation on the retina, visual cortex, and the X and Y cell populations of the lateral geniculate nucleus. Efforts should be made to develop pharmacologic or surgical procedures that are potentially applicable to humans and can produce post

critical period improvement in visual function or eliminate susceptibility to the effects of deprivation.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Amblyopia," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have all been designated as Program Development Priorities and include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Development Priorities

- Develop methods for large-scale screening of vision in very young children to detect abnormalities at an age when treatment is most likely to be effective.
- Improve clinical methods for evaluating vision in young children, emphasizing reliable, simple, and inexpensive methods to assess better the need for treatment of amblyopia in individuals and to monitor treatment.
- Characterize better the nature of amblyopic vision and improve the classification of forms of amblyopia, particularly with respect to prognosis for successful treatment. Study the natural history of amblyopia, with special attention to defining the age limits of susceptibility to various forms of total and partial visual deprivation and various forms of treatment.
- Support efforts to obtain histopathologic correlation in patients with amblyopia.
- Conduct investigations (including clinical trials) of new treatments for amblyopia.
- Expand the inventory of tests, both subjective and objective, of visual function in amblyopia and other sensory disorders.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

VISUAL PROCESSING AND AMBLYOPIA

Disorders

AMBLYOPIA

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Development Priorities			
A. Develop methods for large-scale screening of vision in very young children for detection of abnormalities at an early age.	2	1	3
B. Improve clinical methods for evaluating vision in young children to assess better the need for treatment of amblyopia and monitor treatment.	0	3	3
C. Characterize nature of amblyopic vision; improve classification of forms of amblyopia; natural history of amblyopia.	6	3	9
D. Support efforts to obtain histopathologic correlation in amblyopia.	0	2	2
E. Conduct investigations of new treatments for amblyopia.	0	3	3
F. Expand inventory of tests of visual function in amblyopia/other sensory disorders.	1	3	4
Subtotal Grants	**9**	**15**	**24**
(% of Program)	**(3)**	**(18)**	**(7)**
Total Estimated Cost	**$646,000**	**$1,706,000**	**$2,352,000**

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4

SENSORY NEURO-OPHTHALMIC DISORDERS

INTRODUCTION

NEUROGENIC IMPAIRMENT OF vision occurs in a variety of diseases, some of which are commonly encountered in ophthalmic practice. Lesions in the optic nerve, chiasm, tract, and geniculo-calcarine pathway produce characteristic alterations in visual acuity or visual field that may permit the clinician to localize the malfunction. However, identifying the disease responsible for the lesion may prove difficult or impossible, despite careful analysis of clinical and laboratory data. In addition, even when the lesion is located and the disease identified, the clinician is likely to be frustrated because therapy is unavailing or unavailable. Ignorance of the natural history of these diseases makes accurate prognosis difficult.

Many neuro-ophthalmic sensory disorders are temporarily or permanently disabling. Thus, their impact on individual patients is familiar to ophthalmologists, neurologists, and neurosurgeons. The impact of these diseases on the health of the public, however, is largely unknown because little descriptive epidemiologic data are available and then only for some disorders in a few defined populations.

Nonetheless, these neuro-ophthalmic disorders may be viewed as an "experiment of nature," offering opportunities for investigators to learn about the structure and function of the human brain and visual system. With the aid of ancillary radiological and electrophysiological techniques, better correlation between the clinical features of the disease and the location and nature of the lesion is now possible in living individuals.

Not only ophthalmologists, but neurologists, neurosurgeons, internists, and pediatricians are widely interested in the neuro-ophthalmic sensory disorders. These disorders by their nature, imply brain dysfunction, and they may be expressions of many different neurological and systemic disorders. Clinical and laboratory research in sensory neuro-ophthalmology not only relates to oculomotor and retinal disorders but to a variety of diseases of the central nervous system (including stroke, multiple sclerosis, and brain tumors), diseases of the aged, diabetes, and nutritional and toxicological disorders.

SUBPROGRAM OBJECTIVES

- To understand the natural history, epidemiology, etiology, and pathology of optic neuropathies.
- To develop and evaluate methods for treating optic neuropathies.

OVERVIEW OF CURRENT RESEARCH SUPPORT

Research in Sensory Neuro-Ophthalmic Disorders is supported by NEI as well as by the National Institute of Neurological and Communicative Diseases and Stroke. However, support for research in this field is somewhat limited, as indicated by the fact that NEI funded only one grant at a total cost of $74,000 in this subprogram in FY 1981.

RECENT ACCOMPLISHMENTS

In recent years, research into neurogenic disorders of vision has emphasized common diseases, including optic atrophy, papilledema, optic neuritis, ischemic optic neuropathy, and tumors of the anterior visual pathway.

The results of recent research have helped physicians recognize retinal changes associated with optic atrophy. The findings have also helped clarify the anatomical basis of the changes seen ophthalmoscopically. The use of red-free light and ophthalmoscopic and photographic techniques, which produce well focused and contrasted images of the posterior pole, has led to the detection and analysis of changes in the thickness of the retina due to drop-out of retinal nerve fibers resulting from lesions in the anterior visual pathway. This procedure has proved a powerful tool for detecting and localizing lesions and distinguishing between normal and atrophic optic nerves.

Experiments in primates have explained the striated appearance of the normal nerve fiber layer.[1] The Müller cell processes produce glial tunnels that divide the axons into bundles, thus creating a striated appearance. Lesions produced in the retina were correlated with histopathological changes by light and electron microscopy.[2] Changes were first seen ophthalmoscopically and histopathologically one week following xenon arc photocoagulation of the retina. One month later, groups of axons had been completely absorbed. Degeneration of ganglion cells, which inevitably follows interruption of their axons anywhere between the retina and the geniculate, was also investigated in monkeys. Surprisingly, degeneration of ganglion cells began no sooner with photocoagulation lesions in the fundus than it did with transection of the optic nerve in the posterior orbit. The changes became visible three weeks after injury and appeared complete at six weeks. The site of the injury in the optic nerve does not appear to affect the timing of ganglion cell degeneration. Photocoagulation experiments also have provided insight into the vertical stratification of axons in the retina. In contrast to the results of an earlier study[3] (using local injections of radionucleotide into the retina), which showed that the stratigraphy of axons was not related to the location of cells of origin, a photocoagulation study[4] showed that axons arising from ganglion cells in the macular region assume the most superficial position near the disc.

Experiments have also helped clarify the changes in optic atrophy. Although clinicians have long assumed that there is a decrease in the vasculature of the optic nerve head in optic atrophy, several studies have shown that the vascular bed is normal in this disease. The atrophic appearance of the optic nerve head results from changes in the way the reactive glial tissue reflects light.[5] Reduction in vascularity does not seem to be a consequence of optic atrophy in animal models, and there is some evidence that this is also true in human optic atrophy.

Swelling of the optic nerve head is an important pathological sign. For decades, the pathogenesis of optic nerve swelling (papilledema) associated with increased intracranial pressure was presumed to be vascular, and the edema was thought to reside between the axons. Recent research has radically altered these concepts.[6–8] Papilledema may result not from the accumulation of intercellular fluid but from the distention of axons, which appears to be due to stasis or a damming of axoplasmic flow. Of course, altered axoplasmic flow also occurs in other disorders that may or may not be associated with disc swelling. The axoplasmic distention theory explains why papilledema does not occur in atrophic discs, which consist of dead axons and therefore cannot swell. Because the slow phase of axoplasmic flow occurs at a rate of only about a millimeter a day, it is easy to understand why papilledema develops or recedes slowly. Initially the optic nerve usually functions normally in papilledema despite distention of its axons; swollen axons can continue to function until the cell membrane is extensively damaged. The impaired axoplasmic flow in increased intracranial pressure is probably due to constriction of the optic nerve by elevated pressure in the subarachnoid space at its distal end. Surgical relief of papilledema by cutting the optic nerve sheath, first shown experimentally in monkeys, is now possible in humans. Several reports from different centers have indicated that this method is effective.[9–11] How it works is controversial, probably because of limited information about the histopathological changes in the nerves that have been treated.

The mechanisms by which chronic papilledema produces visual loss are presumed to be vascular but are not completely understood. Subretinal neovascular membranes[12] and optic nerve infarction[13] recently have been recognized as mechanisms by which papilledema may cause visual loss, but these are unusual.

Ischemic optic neuropathy is an important neuro-ophthalmic disorder of middle and late life. Continuing clinical and laboratory investigations have expanded the understanding of this disease and the clinical settings in which it occurs. The electrophysiological characteristic of ischemic optic neuropathy is reduced amplitude of the visually evoked potential (VEP) instead of the altered latency characteristic of the more widely studied inflammatory and demyelinative optic neuropathies.[14] Surprisingly, clinical experience has suggested a poor correlation

between ischemic optic neuropathy and the occurrence of atheroembolic disease. Autopsy material on the nonarteritic instances of ischemic optic neuropathy is scarce. However, a recent histopathological investigation of a patient who was not evaluated in life indicated that the ischemic optic neuropathy found at autopsy involved posterior portions of the optic nerve and was due to emboli. [15]

Optic neuritis is the optic nerve disorder receiving the most attention from clinicians and investigators. Although it is impossible to determine whether multiple sclerosis is responsible for apparently uncomplicated optic neuritis in individuals, the prognosis has been investigated in groups of patients. The studies are difficult to compare because they used different criteria and because some studies were retrospective and others prospective. However, the evidence suggests that at least one-third of patients with uncomplicated optic neuritis develop multiple sclerosis. Other indications of multiple sclerosis generally follow within five years, and the risk appears greater in some parts of the world than in others. Age, sex, recurrences of optic neuritis, and the time of year when the attack occurs may all be correlated with the later development of multiple sclerosis. [16,17]

Electrophysiological testing has been extensively applied in optic neuritis and multiple sclerosis. The VEP to pattern-shift stimuli in these diseases shows a delay in the major positive component. [18,19] Changes in peak amplitude are also commonly seen. Although the visually evoked potential is of small value in obvious cases of neuritis, it may prove helpful in distinguishing optic neuritis from tumor or hysteria, for it is sometimes difficult to distinguish among these conditions, during their acute phase. The VEP may also be used to detect "healed" optic neuritis. Surprisingly, while the VEP amplitude generally recovers after an attack of optic neuritis, latency abnormalities persist in the majority of patients. Abnormal VEPs are highly prevalent among patients with multiple sclerosis and are found in many patients who do not have a history of optic neuritis. An abnormal VEP can also occur in multiple sclerosis patients who have no clinical evidence of an optic neuropathy. Although good histopathological correlation is lacking, VEP is assumed to be useful for detecting lesions in the anterior visual pathway in patients with nonocular evidence of multiple sclerosis. Contrast sensitivity measurement has also proved to be a means of measuring visual function and dysfunction in neuro-ophthalmic disorders in general and in patients with optic neuritis in particular. [20–22] As is the case with VEPs, most patients who recover from optic neuritis continue to show abnormal contrast sensitivity. Some of the contrast sensitivity abnormalities detected in multiple sclerosis patients and patients who have had optic neuritis are compatible with the kinds of dysfunction found in optic nerve disease, but others, such as selective impairment of certain spatial frequencies and orientationally specific contrast sensitivity losses, are more suggestive of retrogeniculate lesions. [23]

There has been considerable immunologic and virologic research on optic neuritis and multiple sclerosis. The results of studies of histocompatibility antigens seem inconclusive, for variations exist among populations in different parts of the world. A B-cell alloantigen, BT101, is highly prevalent among multiple sclerosis patients but is found in only about one-third of controls. In one study the risk of developing multiple sclerosis after optic neuritis appeared to be greater in patients who were positive for the HLA antigen BT101. [17] Some investigators have concluded that histocompatibility antigen testing cannot distinguish patients with optic neuritis from patients with multiple sclerosis, [24] whereas others have concluded that certain histocompatibility antigens that occur with increased frequency among multiple sclerosis patients are not found with greater frequency among optic neuritis patients, as compared with controls. [25]

The BT101 antigen (closely related to BRW2) also is found in Goodpasture's syndrome, [26] an immune disorder involving the lung and kidney with exacerbations and remissions reminiscent of those in multiple sclerosis.

Elevated serum levels of antibodies to measles virus occur in multiple sclerosis and optic neuritis, and measles virus-specific immunoglobulin is found in the cerebrospinal fluid of patients with multiple sclerosis and with uncomplicated optic neuritis. [27,28] Of particular interest is the demonstration of myelinotoxic cerebrospinal fluid in multiple sclerosis patients. During acute exacerbation, 60 percent of these patients had cerebrospinal fluid that produced myelinotoxicity in the optic nerves of tadpoles when it was injected adjacent to the nerves. [29] The myelinotoxicity in the patients did not correlate with immunoglobulin levels in the cerebrospinal fluid. Further, 15 percent of patients with other neurological diseases also had myelinotoxic cerebrospinal fluid. Cell-mediated demyelination has been studied in the intraocular myelinated fibers that are a normal feature of the retinas of certain rodents and lagomorphs using passive transfer of autologous sensitized lymphocytes and antiserum from rabbits with experimental allergic encephalomyelitis. [30,31]

Scientific interest has continued, and perhaps expanded, in optic nerve tumors, probably because of uncertainty about their biology and management. Optic nerve meningiomas are being increasingly recognized. The characteristic clinical picture of some tumors involving the sheath of the optic nerve has been well characterized. Computerized tomographic (CT) scanning has improved remarkably the ability to diagnose optic nerve tumors. The intro-

duction of fine-needle aspiration biopsy using CT scanning for "guidance" offers a potential for biopsy previously not possible without major neurosurgical or ophthalmological exploration.[32,33] Numerous radiological reports have documented the appearance of the normal, inflamed, papilledematous, and tumorous optic nerve, but the status of an optic nerve cannot be established confidently without biopsy.

Reports indicate that optic nerve gliomas, probably the most controversial tumors of the anterior visual pathway, have different characteristics depending upon whether or not the patient has neurofibromatosis.[34,35] The differences observed between the two groups in the location, growth patterns, and tendency to involve the chiasm conceivably may explain the variations in tumor behavior and may have implications for management. Several reports of individual cases[36,37] have suggested that some meningiomas arising primarily within the orbital portion of the optic nerve sheath may be amenable to surgery. Previously, it was assumed that the removal of the tumor resulted in loss of vision.

Interest has increased also in the traumatic optic neuropathies, which usually follow blunt head trauma. There has been little agreement about how they should be managed. Although a fracture can occasionally be demonstrated, a recent report described the autopsy findings in such a case, in which there was a focal infarction of the optic nerve.[38] A fracture visible with the naked eye at autopsy could not be demonstrated in the excised specimen by sophisticated radiographic techniques. Several reports suggest that successful decompression of the optic canal is possible using "extracranial" microsurgical techniques. Transantral and transethmoidal techniques are both feasible.

Much has been learned about the suprastriate or extrastriate levels of visual processing. Developmental dyslexia, a prevalent but poorly defined and little understood disorder, has been associated with brain malformations in the few cases carefully studied by histopathological techniques. This disorder has also been studied by BEAM, a new electrophysiological method.[39–41] Information from multiple scalp recordings of the electroencephalogram and various evoked potentials are condensed and displayed as colored images on a television screen. These computer-generated displays provide temporal and spatial information on brain processing, which provide clues to the nature and location of the dysfunction. Such information may not be obtained by conventional electrophysiological and radiological methods. BEAM studies of a series of dyslexics showed abnormalities in activity implicating wide areas of the left hemisphere and bimedial frontal structures.

Extrageniculostriate vision, long recognized in animals, has been increasingly documented in man.[42–44] In one study, patients with discriminatory function in blind hemifields had undergone hemidecortication in early life for infantile hemiplegia and seizures.[45] Their residual visual function may be explained by anomalous circuitry. However, "residual" visual function in the blind hemifield of adults with acquired lesions indicates that the mature human visual system has a surprising degree of plasticity. Tectal structures are presumably responsible for at least some of the retained functions. Interaction between mirror image areas of the two hemifields apparently occurs in normal individuals and patients with occipital hemianopia, even when there are no posterior callosal connections between the hemispheres.[46–49] This interaction is absent in tract hemianopias.

Interest has continued in visual agnosia (impaired visual recognition) and alexia (reading impairment due to brain lesions), which can be studied profitably only in humans. Meticulous clinical examination of individual patients remains the standard investigative technique. Although once questioned, the existence of visual agnosia seems well established. This disorder results from interruption of the inferior longitudinal fasciculi.[50]

Recent clinical and pathological investigations in man have attempted to localize color vision, face recognition, stereopsis, and topographic functions in the brain. The first two functions are often both impaired when lesions involve the inferomedial occipitotemporal regions bilaterally.[51–53] Topographic memory probably is impaired by similar lesions. The neuropathological substrate of stereopsis remains undetermined despite several investigations.

Visual hemineglect traditionally has been associated with parietal lobe lesions, especially in the right hemisphere. Hemineglect may be difficult to distinguish from hemianopia. Evidence indicates that neglect, once thought to represent inattention, may result in some cases from hypoarousal of one hemisphere[54] or from some motor deficit (intention defect).[55] Studies in man and animals show that lesions in multiple areas, such as brainstem, subcortex, and cortex, are capable of producing neglect. However, parietal lesions appear to produce neglect most consistently and most severely in man. In related studies, intracellular recordings in monkeys have shown that a neural mechanism in the parietal lobe establishes and shifts visual attention.[56]

RESEARCH NEEDS AND OPPORTUNITIES

Research in sensory neuro-ophthalmic disorders has in some ways followed a paradoxical course. Although individual diseases have been investigated extensively, few studies have been designed to measure their incidence and prevalence. The epidemiologic approach is exceedingly important. Epidemiological data for different populations in various areas of the United States, and perhaps the world, could demonstrate variations in the prevalence and incidence of these disorders. Information from descriptive and analytic epidemiologic studies could provide clues to etiology and pathogenesis, and point to other types of potentially fruitful research.

Such studies could lead not only to the genetic, infectious, toxic, or nutritional factors important in the causation or prevention of neurogenic disorders of vision, but suggest how research funds should be allocated.

The epidemiological investigation of nonfatal disorders in highly mobile populations is difficult. To develop useful estimates of the rates of disease occurrence, it is necessary to have a fairly complete identification of affected individuals, and to be able to measure the population at risk at a point in time (for prevalence) and over a time period (for incidence). This is more easily accomplished in countries with nationalized health care systems such as Great Britain and Israel, and in populations that tend to be served by a single institution (such as the population of Olmstead County, Minnesota) or are isolated geographically (such as the Chammoro of Guam). Unfortunately, in the United States, the more closely a population fits the ideal for investigation, the smaller it is likely to be and therefore the less likely to produce reliable data.

A major effort would be required to identify suitable populations, establish a working relationship with those care providers who can recognize individuals with neurogenic disorders, and develop a mechanism for the collection, storage, and retrieval of relevant data over the study interval. The study design should permit the collection of other pertinent information that may help to provide epidemiological clues. For example, the patient may also have other ocular, neurological, or systemic disorders. A follow-up investigation of patients should be arranged to permit review of the accuracy of diagnosis.

Although there have been a few prospective studies on patients with optic neuritis, other important neurogenic disorders of vision have been neglected. Long-term prospective studies of patients who are carefully evaluated at the inception of a study can prove valuable in learning about disease prognosis and in identifying factors to predict the course of the disorder in individuals. Such studies should be conducted by neuro-ophthalmologists in conjunction with colleagues in related disciplines. The disorders of primary importance are optic neuritis, ischemic optic neuropathy, primary tumors of the optic nerves, and transient monocular blindness.

There is no treatment of established value for any of the optic neuropathies. For example, optic neuritis is usually treated with corticosteroids or adrenocorticotrophic hormone. However, this treatment has not been fully evaluated, since the studies that have been performed have involved small numbers of patients. It seems desirable to establish carefully controlled prospective studies in which the short- and long-term effects of treatment can be evaluated. A large, multicenter, randomized clinical trial is needed to determine the value of corticosteroids versus placebo in patients with isolated optic neuritis and in those with optic neuritis and multiple sclerosis. Visual acuity, color vision, perimetry, and psychophysical tests of visual function should be performed before and after treatment. The study period should extend at least six months to determine the effect of treatment on visual function. If positive treatment results are seen for the six-month period, a more prolonged follow-up of the treated group will be needed to determine the long-term prognosis of the treated and untreated groups.

It is important to learn more about the pathogenesis of ischemic optic neuropathy and its relation to other diseases. With the exception of temporal arteritis, ischemic optic neuropathy does not appear to be related to any other systemic disorder, although essential hypertension may play an etiological role. The investigation of patients with ischemic optic neuropathy should provide for prolonged surveillance to permit the identification of recurrent attacks and determine if systemic ocular or neurological disorders develop later.

Another disorder that straddles both neurology and ophthalmology is transient monocular amaurosis. This symptom is considered a harbinger of stroke in some patients and a reflection of narrowing of the internal carotid artery. Yet, despite an abundance of literature, the pathogenesis of amaurosis fugax is uncertain. Several reports have shown that this symptom may occur in otherwise healthy people.

The implications of transient monocular blindness should be studied in patients of all ages who have such attacks. In addition to standard ophthalmic and neurological evaluations, angiography of the fundus and either direct or indirect visualization of the orbital vasculature and the pertinent portions of the external and internal carotid circulation are needed; the newly developed technique of digital subtraction tomography seems likely to supplant conven-

tional angiography. Studies of platelet function and other hematologic factors that may influence the rheology of the carotid system also deserve investigation. Detailed descriptions of the visual dysfunction should be sought, and meticulous neuro-ophthalmic examination should be made to identify any residue of an episode. A long period of surveillance would be desirable to identify further attacks, recognize any fixed neurological or ophthalmic deficits that develop subsequent to the original illness, and correlate the attacks with the later development of any systemic disorder.

Most of the optic neuropathies and other neurogenic disorders affecting the visual pathway are not associated with fatal processes; therefore, human tissue, while of extreme interest, becomes available infrequently, late in the course of the illness or under other circumstances that minimize the ability to extract important information from the diseased tissues. The value of animal models of the neurogenic disorders of vision cannot be overemphasized. Important animal experiments already have increased the knowledge of the structural basis and pathogenesis of some of the important signs and symptoms in neurogenic disorders of vision. Because of variations in anatomy, animal models primarily should be primates. The latest neurophysiological techniques can permit measurement of visual function rather easily in primates and relieve investigators of the necessity of using behavioral tests of vision that cannot be as easily quantified or performed. Further models of optic neuritis also should be sought.

Attempts should be made to compare by electrophysiological means the function of the animal visual system with various forms of experimentally induced optic neuropathy that have been fully characterized by histopathological techniques. Attempts also should be made to understand fully the cellular basis of the changes observed in the electrophysiological responses in various optic neuropathies.

In addition, nutritional optic neuropathies represent a worldwide problem that remains unclarified despite a wealth of anecdotal information and a small number of experiments. These disorders should be characterized in experimental animals through the collaboration efforts of nutritionists, ophthalmic pathologists, electrophysiologists, and neuro-ophthalmic clinicians. Finally, the role of neurotransmitters or neurotransmitter depletion in the pathogenesis and treatment of dysfunction in the visual pathway should be carefully evaluated.

While great strides have been made in understanding normal and disordered visual perception, only the rudiments are known. Clinical and pathological investigations of patients with disorders of higher visual function must be continued and extended. Conventional clinical examinations should be supplemented by newer radiological, metabolic, and electrophysiological methods to pinpoint the location and nature of dysfunction within the central nervous system.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Sensory Neuro-Ophthalmic Disorders," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have all been designated as Program Development Priorities and include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Development Priorities

- Conduct epidemiologic studies of optic neuropathies in the United States.
- Conduct clinical investigations of optic neuritis, ischemic optic neuropathy, and amaurosis fugax, including prospective natural history studies and clinical trials to evaluate methods of treatment.
- Develop animal models of optic neuropathies to correlate electrophysiologic and psychophysiological test results with histopathological characteristics of lesions and test the role of specific nutritional deficiencies, including amino acid precursors of neural transmitters, in the development of optic nerve disorders.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

VISUAL PROCESSING AND AMBLYOPIA

Disorders

SENSORY NEURO-OPHTHALMIC DISORDERS

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Development Priorities			
A. Conduct epidemiologic studies of optic neuropathies in the United States.	0	1	1
B. Conduct investigations of optic neuritis, ischemic optic neuropathy, and amaurosis fugax.	0	3	3
C. Develop animal models of optic neuropathies; correlate electrophysiology, psychophysics, and histopathology; test the role of nutritional deficiencies in optic nerve disorders.	1	3	4
Subtotal Grants	**1**	**7**	**8**
(% of Program)	**(1)**	**(8)**	**(2)**
Total Estimated Cost	**$74,000**	**$710,000**	**$784,000**

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OCULAR MOTILITY AND STRABISMUS

OCULAR MOTILITY AND STRABISMUS

THE FOLLOWING SIX chapters are concerned with all aspects of eye movements, including the sensory inputs, neural processing and integration, as well as the responses and properties of the extraocular muscles that perform eye movements. Proper functioning of all of these systems is essential for scanning the environment, aligning the two eyes to allow stereopsis; and permitting steady fixation and pursuit movements to perceive fine detail.

Casual observation of eye movements of others provides little information about the way the eyes move, other than that the eyes appear "straight" and capable of aligning themselves upon a point of fixation. More detailed observation and precise recordings reveal two basic types of eye movements. Those in which the two eyes move in the same direction—up, down, right, and left—are called conjugate eye movements. Those in which the eyes move in opposite directions are called vergence eye movements and refer principally to convergence and divergence. Conjugate eye movements seem to be largely "prewired" (determined by neuronal connections) and include at least two major types of movements: the saccadic, a fast, sudden refixation of the eyes to a new object, and pursuit, a following movement exemplified by attention to a swinging clock pendulum. These two functions can be studied monocularly or binocularly because the wiring of the system makes the two eyes move in the same direction with some precision. Good peripheral vision is necessary to detect a new object of interest and thus allow an appropriate saccadic response. Good central visual acuity is required to provide steady fixation and good pursuit movements. Thus, the sensory aspect of vision is necessary for the eyes to move appropriately with precision. If the eyes do not see normally, other factors that normally are less significant begin to overwhelm the eye movement system. These include position sense from the middle ear, sound localization of objects, and voluntary eye positioning. The latter mechanisms can be used experimentally to evoke eye movements in the dark and thus study submechanisms of conjugate eye movements.

Conjugate eye movements require only one eye to function normally, but version eye movements require the entire visual system to function perfectly. If the focus of either eye is significantly impaired, the precision of convergence or divergence will be degraded. Thus, the sensory input has significant bearing on these movements. Poor vision in either eye of an infant will degrade the version system, the eyes will not be aligned, and may often result in a significant strabismus. The reverse is also true; that is, failure of the vergence system and ensuing misalignment of the eyes may cause degradation of vision in one eye, resulting in amblyopia.

This information is presented to emphasize the composite studies that are described in the following six chapters; namely, eye movements are meaningful only as they respond to stimuli and align the eyes so as to allow the brain to assemble a three-dimensional picture and to keep the eyes on one small facet of that picture, regardless of whether the facet or the observer moves. Although a great deal is known about conjugate movements, relatively little is known about version eye movements. As more is learned about convergence and divergence, attention will be redirected to the saccadic system to study the interactions between the two systems. These studies are aimed at finding causes and treatments of one of the most common human ocular afflictions—disturbances of binocular vision.

5

NORMAL AND ABNORMAL DEVELOPMENT

INTRODUCTION

THE DYNAMIC PROCESSES involved in the embryogenesis of the anatomic subsystems serving ocular motility and the physiologic maturation of these systems have been incompletely studied in both laboratory animals and human infants. Moreover, the long-term visual consequences of abnormal anatomic development resulting from perinatal insults, abnormal visual environmental stimuli in infancy, or inherited anomalies of the oculomotor system are still largely unknown. The knowledge that variations in environmental conditions may interfere with normal maturation of both sensory and motor systems is highlighted in all the recent developments in neurobiology.

Congenital disorders of the oculomotor system are significant problems because they often handicap an individual for his or her entire life. Furthermore, developmental disorders of the oculomotor system are occurring more frequently because of the high percentage of premature and "small-for-gestational-dates" infants who survive as a result of improved neonatal care. Unfortunately, no longitudinal studies documenting the visual disorders of these "at-risk" infants have been completed.

Although research on developmental oculomotor disorders should include both basic science and clinical studies, it is important to note that studies have been limited primarily to the embryogenesis of various anatomic substrates of the oculomotor system. Little clinical or laboratory research has been conducted on the normal embryogenesis of extraocular muscles, cranial nerves, or intracerebral pathways of normal human fetuses. Much of the classic descriptive embryology as described by light microscopy is incomplete or in error. A renewed interest in the maturation of normal anatomic and physiologic systems is essential to a more complete understanding of developmental oculomotor defects in man.

SUBPROGRAM OBJECTIVES

- To define the anatomic physiologic maturation of the subsystems of the oculomotor system.
- To extend clinical studies of the maturation of various oculomotor subsystems.
- To assess the long-term oculomotor consequences of raising infants in various visual environments.
- To define and delineate the various adaptive oculomotor strategies utilized by children to overcome congenital deficits such as congenital hemianopsia and various conditions associated with significant visual loss.

OVERVIEW OF CURRENT RESEARCH SUPPORT

A review of the NEI grant portfolio indicates that research on normal and abnormal development of the oculomotor system has had little grant support in the last several years. In FY 1981, the NEI supported five research grants in this subprogram at a total cost of $439,000. This entire area does not appear to have been appropriately articulated in previous National Advisory Eye Council planning

reports. At present, the objectives of the subprogram, which are listed above, are not being met adequately by current research. This entire field needs additional research support.

RECENT ACCOMPLISHMENTS

Definition of at least two separate anatomic systems serving optokinetic nystagmus in monkeys has provided interesting insights to several disorders of vision.[1] Optokinetic nystagmus (OKN) may be generated by a foveal-geniculocalacrine system or a more primitive pathway involving the peripheral retina, the extrageniculate striate system, and brainstem centers such as the accessory optic nucleus.[2] Characteristically, this more primitive system shows a unique unidirectional preference of generated OKN under monocular conditions; that is, OKN is generated as the stimulus moves from the temporal to nasal fields, but not in the reverse pattern. There is convincing evidence that motion-sensitive retinal ganglion cells are the input stage of the optokinetic loop in the rabbit, because their firing rates have been shown to correlate with the velocity of OKN.[3] This unidirectional OKN has been identified in patients with amblyopia and achromatopsia. These observations suggest that when central vision is interfered with at any level, be it retinal or cortical, the more primitive form of OKN generated by peripheral stimuli predominates. This may allow further investigation of the importance of the human extrageniculate striate system, especially in infants where plasticity may allow utilization of this system for some visual functions.

Preliminary studies of vestibulo-ocular system maturation in human neonates have been completed.[4,5] The studies suggest that this system matures much earlier than other oculomotor systems.[6] Maturation may be significantly delayed in premature infants or "small-for-gestational dates" infants. Whether these delays result in long-term disorders of ocular vestibular function has not yet been studied. However, preliminary data suggest that specific patterns of delayed maturity may be associated with some forms of horizontal comitant strabismus. Moreover, several transient supranuclear eye movement disorders occur in healthy neonates, and delays in the maturation of the ocular vestibular system could be important in the genesis of some abnormal eye movements of infancy.[7] The exact role played by genetic, compared with environmental, factors in these patterns of maturation delay are undefined.

Young laboratory animals have been raised in a number of abnormal visual environments, which result in misalignment of optical axes and ocular oscillation. Dark-reared animals display both a divergence of the visual axes and a cyclotorsional deviation.[8] Although these misalignments generally resolve once the animal is exposed to normal lighting, the long-term consequences of this early deprivation have not been completely defined. Misalignment of the visual axes and ocular oscillations have also been reported in animals raised in strobe lights.

Preliminary studies have been carried out on the developmental sequences in the maturation of central visual nuclei. The dynamic nature of normal embryogenesis of other portions of the oculomotor system has also been investigated. This is especially relevant to studies of the normal development of extraocular muscles. These studies suggest that the extraocular muscles originate at the corneal-scleral limbus as relatively undifferentiated mesodermal tissue. The orderly arrangement of these muscles is not complete at birth, and the location of the normal muscle insertion in relation to the limbus continues to change during the first several months.[9] This observation has obvious significance for the ophthalmic surgeon performing early strabismus surgery.

RESEARCH NEEDS AND OPPORTUNITIES

Opportunities to study the development of the oculomotor system exist in premature infants in neonatal intensive care units. However, studies in these nurseries are difficult to perform since the infants are frequently critically ill.[10] Moreover, ethical problems are often a serious obstacle in any study involving "at-risk" infants. This research should be encouraged where feasible, since the data accumulated would increase the understanding of the genesis of common oculomotor disturbances in normal children.

Development of techniques that would permit quantitative analysis of eye movements in the newborn nursery would be an important advance because current techniques are not applicable to this setting. Neonatal eye movement recordings would contribute significantly to knowledge of the maturation of various oculomotor subsystems. Specifically, very little data are available on the timing and nature of the maturation of the pursuit, saccadic, fixational, and even the ocular vestibular systems. Normative data would provide the framework for understanding how delays or arrests in maturation may lead to disorders of ocular motility. A significant number of strabismic disorders in children may,

at least in part, result from environmental insults to or genetic errors of the elemental systems of oculomotor control.

Recent clinical observations of the VOR response of children with various forms of infantile esotropia suggest that disturbances of the ocular vestibular system may be important in strabismic disorders. The auditory brainstem potential may prove to be a useful tool to investigate brainstem function in oculomotor disorders.[11] Localization of specific areas of brainstem dysfunction would greatly enhance the understanding of oculomotor disorders.

The normal newborn infant may manifest a frank misalignment of the visual axes and not have subsequent problems. This neonatal misalignment may take the form of a simple tropia or a more complicated disorder such as skew deviation. Little is known about the process whereby the normal infant establishes alignment and fusion, over what period of time transient oculomotor disturbances resolve, and when a tropia is fixed and no longer potentially reversible. The natural history of the normal process of fusion should be documented to understand better the pathogenesis of some forms of strabismus and define the appropriate timing for treatment.

The apparent visual handicap in the infant with congenital hemianopsia or visual cortex damage is manifestly less severe than in the adult with a comparable acquired defect. Some of this difference may be due to the infant's ability to utilize the extrageniculate striate system, and also to its utilization of adaptive oculomotor strategies in a compensatory effort. More complete delineation of these adaptative strategies might be important for rehabilitation of older patients with acquired oculomotor defects.

The oculomotor adjustment to blindness has been incompletely studied. The gain in the vestibular system response appears much greater in the blind infant. Whether this plays a role in the general motor maturation delays seen in blind children is not certain. However, the frequently associated cerebellar lesions may contribute to the marked motor retardation of infants suffering from Leber's amaurosis.[12] The response of the oculomotor system to blindness needs further study.

Plasticity has been demonstrated in almost all of the oculomotor subsystems, and the cerebellum is involved in some way, although the exact mechanism is not known. The effect of destructive cerebellar lesions in young animals or human infants on oculomotor plasticity has not been investigated. Such studies could be useful for understanding the mechanisms responsible for plasticity.

Studies of the oculomotor consequences of visually deprived infant animals have been previously cited.[8–13] Less complete deprivation, but for prolonged periods, might also result in oculomotor disturbances. It is important to investigate whether comparable human disorders occur, especially in the premature infant raised for several weeks in intensive-care nurseries.

The embryogenesis of specific oculomotor subsystems has not been detailed, even in animals, and requires further investigation. Eventually it would be advantageous to produce animal models of prenatal insults to the oculomotor system, for some common human oculomotor disturbances clearly result from such insults (for example, Duane's syndrome).[14] In fact, the question of whether nuclear aplasia can even occur as a primary event must be answered to understand congenital disorders such as the Mobius syndrome. Further, careful pathologic studies of oculomotor disorders in humans should be encouraged.

The normal and abnormal development of the oculomotor system needs to be studied much more extensively than it has been to date. Basic laboratory research is needed, as well as research in human infants. Studies with currently available techniques should be expanded and the methodology extended to include quantitative ocular movement recordings in the nursery, evaluation of brainstem function in patients with oculomotor disorders, and intracellular labeling of developing animals.

The field of developmental biology has expanded rapidly in the last decade. Although the skills and research techniques of basic scientists in this area are not generally understood or used by the clinical community, the importance of understanding normal maturation processes to improved comprehension of the factors responsible for visual sensory and motor abnormalities is obvious. A major commitment should be made to bring young clinicians with an interest in developmental biology into the field of pediatric ophthalmology. Research fellowship programs in this discipline should be encouraged where appropriate personnel are available to provide such training. Although most research in this area concerns strabismus and amblyopia, a multidisciplinary approach should be encouraged so that the dynamics of developmental factors are more clearly applied to clinical problems.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Ocular Motility and Strabismus: Normal and Abnormal Development," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have been grouped under two

headings: Program Base and Program Development Priorities.

The Program Base consists of an area of ongoing research in which the current level of activity is considered adequate. Nonetheless, additional research grants in this area may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Base

- Continue studies, in infants and animals, on the oculomotor effects of visual deprivation (both partial and complete) and other abnormal visual stimulation.

Program Development Priorities

- Determine whether early experience in an abnormal visual environment increases the risk of comitant strabismus, refractive error change (myopia), or loss of stereoacuity.
- Develop quantitative eye movement recording techniques to study normal and abnormal development of eye movement patterns in neonates and young children.
- Determine the frequency of temporary strabismus in neonates and the normal establishment of fusion.
- Evaluate the adaptive oculomotive plasticity of infants and animals to disorders of the visual and oculomotor systems, including the cerebellum.
- Describe, at subcellular and cellular levels, the development of the extraocular muscles and associated cranial nerves.
- Describe, at molecular, cellular, and behavioral levels, the development of the oculomotor system, including sensory inputs and the cerebellum.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

OCULAR MOTILITY AND STRABISMUS

NORMAL AND ABNORMAL DEVELOPMENT

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Base			
A. Continue studies on the oculomotor effects of visual deprivation and other abnormal visual stimulation.	2	1	3
Program Development Priorities			
A. Determine the relationship between early abnormal visual environment and the risk of comitant strabismus, myopia, or loss of stereoacuity.	0	2	2
B. Develop quantitative eye movement recording techniques in neonates and young children.	0	2	2
C. Determine frequency of temporary strabismus in neonates/normal establishment of fusion.	0	1	1
D. Evaluate adaptive oculomotive plasticity to visual/oculomotor disorders.	0	2	2
E. Describe at cellular and subcellular levels the development of extraocular muscles/associated cranial nerves.	0	2	2
F. Describe at molecular, cellular, and behavioral levels the development of oculomotor system.	3	2	5
Subtotal Grants	**5**	**12**	**17**
(% of Program)	**(2)**	**(14)**	**(5)**
Total Estimated Cost	**$439,000**	**$1,227,000**	**$1,666,000**

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6

CONJUGATE EYE MOVEMENTS

INTRODUCTION

THIS CHAPTER DISCUSSES research on all aspects of the neural systems that produce or control conjugate eye movements. Such research requires an understanding of how neural circuits process signals at many levels of the central nervous system and involves a wide variety of research approaches and techniques from diverse disciplines such as anatomy, physiology, neurochemistry, psychology, biocybernetics, and aerospace medicine.

Knowledge of the central circuits that control eye movements increased rapidly in the 1970s because of two principal factors. One is the development of techniques for recording from neurons and fibers in alert animals able to make normal eye movements. The other is the use of new tracers to discover new oculomotor areas of the brain stem and cerebellum. The normal behavior of eye muscles and their motoneurons is now reasonably well understood. Although progress in understanding the vestibulo-ocular reflex has been excellent, especially in describing the behavior of the vestibular apparatus, several important pieces of the picture are missing, such as the contributions of the reticular formation and flocculi. Knowledge of the optokinetic system in the rabbit is fair, but many aspects of the system's central connections from the accessory optic system to the vestibular nuclei, and the role of the transcerebellar pathways, remain to be clarified. Almost nothing is known about these pathways in primates. Understanding of the saccadic and pursuit systems is very meager. The anatomical and functional relationships between motoneurons and a few immediately-premotor cell types that mediate saccades or pursuit movements are known, but more central circuitry remains poorly understood. Both systems utilize the pattern recognition capabilities of the visual system and the cognitive processing of target selection. These higher processes will not be understood soon, but progress might be expected in the next few years in clarifying the format of the commands from such higher levels and how the brain stem circuits transform those commands into the desired eye movements.

As for the clinical aspects, progress is being made by improved quantification and analysis in examining patients. Facts gathered in basic research are being integrated into models that provide clinicians a working hypothesis for understanding their patients' oculomotor disorders. It is still not certain, however, just what criteria should be used for population studies of the various classes of eye movements to distinguish normal from abnormal movements. In addition, not all of the subsystems that produce conjugate eye movements have been delineated and characterized; nor is their function understood. For example, the function of microsaccades is not understood. A function of most oculomotor subsystems is to decrease retinal image motion, but just how much motion can be tolerated before various types of visual processing become impaired is not known. Thus, although recent progress has been remarkable, there are many large gaps in the understanding of eye movement control.

SUBPROGRAM OBJECTIVES

- To classify and describe quantitatively all the types of normal eye movements in humans and in animals.
- To discover the neural circuits involved in eye movements and describe how they generate all known types of conjugate eye movements.

- To use this knowledge to improve the diagnosis and treatment of strabismus, to explain the cause of abnormal eye movements, and to find means of preventing and curing other oculomotor disorders.

OVERVIEW OF CURRENT RESEARCH SUPPORT

Thirty-nine research projects in this subprogram were supported by the NEI in FY 1981 at a total cost of $3,277,000. Of these, about one-quarter were devoted to describing eye movements more accurately, determining the appropriate stimuli for them, or examining the influence of eye movements on perception. Most of the remaining projects involved neuroanatomy or neurophysiology. Of this group, a few were devoted almost exclusively to anatomical studies, while others included anatomical tracer studies along with other activities. About one-third of this group contributed to a knowledge of pathways. Of the projects that include neurophysiology, most involved some recording from alert animals, the majority worked exclusively with alert animals, while few involved only studies in anesthetized animals.

Most investigators now work on both alert and anesthetized animals. The most fruitful approach currently seems to be a combination of anatomical studies and single-unit recordings that allow scientists to examine the interrelationships between a structure and its function. These projects cover most of the brain regions known to be important to eye movements and use methods that range from the standard lesioning, recording, and stimulating techniques, to new methods such as the use of 2-deoxyglucose to localize metabolically active sites and injection of horseradish peroxidase into single neurons in alert animals to identify the cell's functional properties and its anatomical projections. In summary, research currently supported by the NEI is helping achieve the above objectives. Progress is not limited by technical or conceptual problems; an increase in manpower would lead to an increase in significant knowledge about the organization and operation of the oculomotor system.

RECENT ACCOMPLISHMENTS

Analysis as a Control System

One all-pervading sign of progress in the last five years is an increased recognition that the methods developed for analyzing nonbiological control systems are equally appropriate, and indeed required, in the analysis of biological control systems such as the oculomotor control system. One advantage of this is that it directs attention to the most important aspects of a system's behavior and indicates what measurements are most suitable for describing that behavior. For the vestibulo-ocular reflex, for example, the ratio of slow-phase eye velocity to head velocity, which is the gain of the reflex, is recognized as the most significant characteristic of the reflex, because it measures the effectiveness of the compensatory eye movements. Another characteristic of this reflex is its bandwidth or time constant. Similar characteristics have emerged in all oculomotor subsystems. These aspects—gain, bandwidth, time constant, and others such as phase shift and stability—now appear routinely in both the basic and clinical scientific literature.

Such descriptors of the normal and abnormal oculomotor subsystems also emphasize quantitative measurement. These measurements have become possible through the improved methods of recording eye movements that have been developed over the last 15 years and are now being used more frequently in the clinic. They result from an increased awareness that only such data permit one to measure the intrinsic properties of the control system being studied. The acceptance of quantitative, analytical concepts is now so complete that it is easy to overlook the significance of their impact.

Describing the oculomotor system as a control system denotes that something is controlled for a purpose. There is general agreement, for example, that the purpose of the vestibulo-ocular reflex is to limit the amount of retinal image motion during head movements and that the purpose of saccades is to put the image of an object of interest on or near the fovea. It is important to recognize these functions because systems with different functions are served, at least in part, by different neural pathways. Thus, it is important that the various functions be identified behaviorally and their unique neural pathways identified, if disturbances of normal oculomotor function are to be identified and have value in localizing a neurological lesion. Furthermore, the behavior of a neuron can be interpreted much more readily if one understands the purpose of the network in which it lies. As a case in point, the pursuit and optokinetic responses serve different

functions and their neural pathways differ in part.[1,2] They are often confused because it is difficult to stimulate the latter without the former. Yet, they must be distinguished if clinical disorders or the behavior of neurons in the central pathways are to be interpreted correctly. The recognition of the importance of dividing the oculomotor system by function is an important conceptual advance, but subsystems exist with functions not clearly defined, and others are not yet recognized. Their clarification is vital because the interpretation of neural data and clinical disorders is impeded by not knowing how many oculomotor subsystems exist or what their functions are.

Once a system's function has been defined, the way is clear to formulate hypotheses which describe how that function might be fulfilled. Systems with feedback or even rather simple dynamic behavior—and this includes all oculomotor subsystems—are sufficiently complex that word descriptions are inadequate; a diagram must be used along with mathematical descriptions of the behavior of the elements in that diagram, if a description is to be useful qualitatively as well as quantitatively. Such hypotheses, commonly called models, are useful scientific tools for interpreting available data and predicting the outcome of further experiments. For the clinician, they provide mechanistic explanations of the eye movement disorders encountered in the clinic, such as gaze paretic nystagmus,[3] internuclear ophthalmoplegia, periodic alternating nystagmus,[4] postsaccadic drifting movements,[5] slow saccades, ocular flutter, and downbeat nystagmus.[3] For the basic scientist, these models provide a working hypothesis for planning experiments. The development of many such hypotheses is perhaps the most outstanding result of using a control-system approach in oculomotor physiology.

The Techniques of Tracers and Recording in Alert Animals

Over the last five years, the main source of progress in the structure-functional aspects of conjugate eye movements has been through the utilization of tracers and recording techniques to study neuronal activity in alert animals. By implanting stimulating electrodes in various locations for antidromic and orthodromic stimulation, it has been possible to establish some of the anatomical connections of the neurons being recorded in alert animals. More complex training paradigms have made it possible to explore cell behavior during a variety of visual and vestibular stimuli and alterations of mental set that expand the dimensionality of the behavior studied to more realistic levels. Tracer techniques have greatly improved in the last five years; they have become more sensitive, more localized, and produce much better resolution. Recently, it has become possible to record intracellularly from cells and fibers in animals that are either entirely alert or sufficiently alert to make certain types of eye movements in response to vestibular stimulation. This allows one to see the signal carried by this cell as it participates in eye movements. Orthodromic and antidromic stimulation can then be used to reveal the connectivity of the cell.[6] In addition, the cell may be injected with a tracer that reveals all of its projections.[7] This type of research, (Figure 1) which combines the two basic techniques mentioned, allows one to know both structure and function in a single neuron, and it should provide essential information about the operation of very important brainstem circuits. The discovery of a number of structures not known to be related to oculomotor control five years ago demonstrates the success of the anatomical techniques; and the identification of the nature of the signals (the modulation of the instantaneous discharge rate with eye and head movements) carried by the neurons of oculomotor structures has provided the basis for a hypothesis of the role of each in controlling eye movements.

The importance of the vestibular nuclei, for example, in voluntary eye movements, as well as the vestibulo-ocular reflex, is now well established.[8] Second-order vestibular neurons not only receive a head-velocity signal from the semicircular canals but also receive and relay to the eye muscle motoneurons commands for fixation and pursuit.[9,10] Many other types of cells in this nucleus participate in various types of eye movements in a manner independent of vestibular nerve input. The nucleus prepositus hypoglossi was not known to be involved with eye movements until tracer studies showed that its cells projected directly to motoneurons.[11] Subsequent study has revealed a strong vestibular input and cells that carry the signals required for all types of conjugate eye movements. Its juxtaposition to the vestibular and abducens nuclei shows that this nucleus plays an important role in preparing oculomotor commands.

The medullary and pontine reticular formations, long known to be vital for eye movements, are now known to contain, respectively, inhibitory and excitatory burst neurons that project directly to motoneurons in a push-pull fashion, creating saccades and other rapid eye movements.[12] These findings clarify the final output pathway for the horizontal saccadic system. Directly on the midline and lying in the raphe nucleus between the rootlets of the sixth nerve, large cells called pause neurons have been discovered that fire at a constant discharge rate but stop during all rapid eye movements. These cells probably inhibit burst neurons, the most dramatic evidence being that stimulation of this area causes global saccadic paralysis.[13] The pause neurons may prevent unwanted burst activity until they pause; thus they control the initiation and

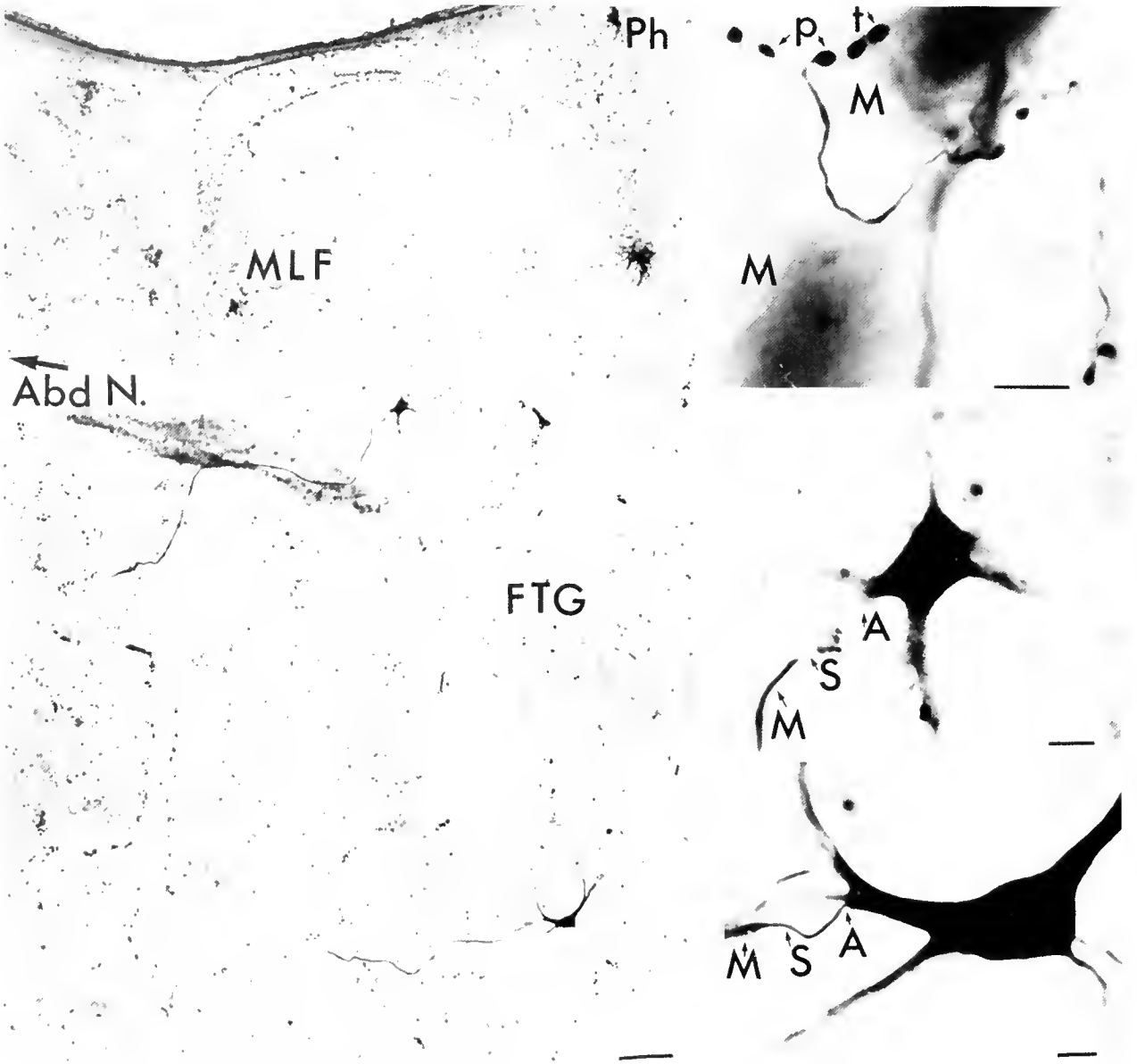

FIGURE 1. An example of correlating structure and function by recording from neurons in alert animals and then staining them with an intracellular tracer. At the left is a coronal section of the cat medulla just posterior to the right abducens nucleus showing two stained cells (center and lower right). A microelectrode filled with horseradish peroxidase (HRP) penetrated the axons of these cells near the left abducens nucleus (abd N.) These axons showed a burst of discharge activity during right saccades and could be identified as inhibitory burst neurons. The axons were then injected with HRP which filled the axon, cell body, and dendrites. The cells appear enlarged at the lower right to illustrate the axon hillock (A), initial segment (S), and medulated axon (M). The upper right inset shows one axonal arborization of one cell in the contralateral abducens nucleus. Boutons enpassant (p) and terminaux (t) are seen contacting the counterstained motoneurons (M) MLF, medial longitudinal fasciculus; FTG, gigantocellular tegmental field; Ph, nucleus prepositus hypoglossi. (Photographs courtesy of R. Baker.)

possibly the timing of saccades.[14] It has been postulated that defective pause neurons might create involuntary saccades such as those that occur in square wave jerks and ocular flutter.[15]

It was long thought that the motor nuclei contained only motoneurons and that they had no axon collaterals. This is now known to be incorrect. A most important finding is that the abducens nucleus contains many cells, called internuclear neurons, which send fibers across the midline and up the contralateral medial longitudinal fasciculus (mlf) to medial rectus motoneurons,[16] relaying to them a copy of the final motoneuron command.[9,10] These findings clarify the nature of eye movement disorders after lesions of the mlf, such as internuclear ophthalmoplegia, and of the abducens nucleus. Structures around the oculomotor nucleus partici-

pate, with cooperation from the vestibular nuclei, in organizing vertical eye movements. Tracer studies have revealed new oculomotor areas such as the interstitial nucleus of the rostral mlf, and recordings from alert animals in this and other nearby nuclei such as the interstitial nucleus of Cajal reveal cells participating in rapid eye movements and maintaining eye position in the vertical direction.[17] These findings suggest how the signals that produce vertical eye movements are organized.

For a long time, little attention was paid to the cerebellum because, upon its removal, animals seemed able to make normal eye movements. We now know that this is wrong. Interest in this structure grew rapidly after it was discovered that cerebellar lesions abolish pursuit,[18] cause saccadic dysmetria, and affect several types of adaptive plasticity.[19–21] The flocculus is especially important in oculomotor control. Floccular lesions in monkeys interfere with pursuit and with visual suppression of unwanted vestibular nystagmus, cause downbeat nystagmus, gaze nystagmus, rebound nystagmus, postsaccadic drifting movements,[22] and a loss of the ability to adjust the gain of the vestibulo-ocular reflex. All of these abnormalities create, or fail to suppress, retinal image motion and help to explain many of the clinical observations associated with cerebellar disorders. Recordings from the fibers and cells in this structure in alert monkeys have provided insight into its role in pursuit and cancellation of the vestibulo-ocular reflex.[23,24] Lesions of the cerebellar vermis, on the other hand, cause saccadic dysmetria and loss of adaptive plasticity of saccades.[21] Neurons in this region also modulate their discharge with saccadic eye movements.[25] These findings also help in interpreting oculomotor disorders in humans.

Important progress has been made in oculomotor pathways descending to the brainstem. The terminal nuclei of the accessory optic tract and the nucleus of the optic tract, for example, are essential for optokinetic movements in rabbits by providing the visual stimulus for such movements.[26] This signal appears to pass through the nucleus reticularis tegmenti pontis to the vestibular nuclei and thence to the ocular motoneurons.[1,27] These findings have led to a much deeper understanding of the optokinetic system in subprímates that now needs verification in primates. Another projection is to the inferior olive and thence to the flocculus on climbing fibers; this pathway seems concerned with plasticity of the vestibulo-ocular reflex, discussed below. Considerable new knowledge of the oculomotor aspects of the superior colliculus has been gained in recent years.[28] Cells in its intermediate and deeper layers burst just before saccades with certain directions and amplitudes, and the activity of some of them seems to reflect the decision process that selects one visual target from others in order to execute a saccade to it.[29] These findings are significant because they give a glimpse into the deeper central processing that bridges the enormous gap between visual perception and motor action. Research has progressed in the last five years on the oculomotor behavior of cells in the internal medullary lamina of the thalamus, which participate in a variety of eye movements in complicated ways that depend on eye position and retinal stimulus location.[30] These cells are important because they may act as a bridge between the very complex behavior of cells in the cerebral cortex and the more readily interpretable behavior of cells in the brainstem.

Recent research has confirmed a role for the frontal eye fields in eye movements. Cells in this region respond to visual stimuli, and this response is greatly enhanced when a monkey decides to make a saccade to a particular visual object.[31] Consequently, a significant amount of neural activity occurs in the frontal eye fields just preceding certain types of saccades. A dramatic loss in oculomotor range when frontal eye field lesions are combined with superior colliculi lesions[32] emphasizes the oculomotor importance of this region. Recent experiments have revealed cells in the parietal lobes that are associated with various type of eye movements in ways that depend on the monkey's state of attention and interest in the object of regard.[33] Many of these cells are also visually activated, and their activity during or preceding eye movements is an attentional enhancement of the visual response.[34] These cells are evidently involved in higher, decision-making processes rather than directing the specifics of the movements.

Treatment of Disorders by Neurotransmitter Drugs

The importance of studying neural transmitters in the oculomotor system was dramatically emphasized by the recent discovery that the drug baclofen, a synthetic analogue of GABA, stops periodic alternating nystagmus, a disorder in which jerk nystagmus to the left is cyclically replaced by nystagmus to the right about once every two minutes.[35] This disorder produces illusory movement of the environment and degrades vision to the point that reading is impossible. Baclofen stops these oscillations and permits normal visual function. Because these drugs are one of the few tools available to alleviate central oculomotor disorders, it certainly seems appropriate to learn more about the neuropharmacology of the system and to search for other such treatments.

Plasticity

Seven forms of plasticity have now been demonstrated in the oculomotor system, and probably more will be discovered. Compensation of nystagmus after an eighth nerve lesion is the form that has been studied the longest but it still defies explanation. Changes in the gain of the vestibulo-ocular reflex is a form that has received great attention in the last 10 years [19,20,36,37] and has been demonstrated in a wide variety of species. At least some types of plasticity are thought to be important in establishing correct eye movements at birth and for maintaining them during growth and in disease states. Since five of the seven forms of plasticity of the oculomotor system are known to be affected by cerebellar lesions, current research projects are examining the cerebellum, especially its climbing fiber input, to learn how the cerebellum is involved. The discovery of these systems has an important influence on clinical diagnosis. The fact that motor function can recover after brain lesions has long been known, but the mechanisms, time course, and range of such compensation have not been known. Also, it has not been realized previously that cerebellar lesions played a significant role in delaying or abolishing such compensation. Thus, this research has direct clinical relevance.

Subsystem Interactions

For many years, it was said that one advantage of studying the oculomotor system was that its subsystems could be studied in isolation. This is true in part; each subsystem has been characterized in suitably restricted conditions. It has been realized recently, however, that more can be learned by studying the interactions between subsystems. An example of this is the optokinetic system; the entire visual environment almost never rotates en bloc relative to a subject's head if the head is stationary, but always does so when the head is turning. Thus, the optokinetic system and vestibulo-ocular reflex are always stimulated together. Failure to appreciate this fact has led to much confusion and misinterpretation of the purpose and beh vior of the optokinetic system, especially in the clinic. As another example, when one follows a moving visual target, one generally does so with a head movement during which the vestibulo-ocular reflex must be prevented from acting. It is believed that the reflex is canceled by a command from the pursuit system, implying that the pursuit system and the vestibulo-ocular reflex are often stimulated together. This idea is supported by the discovery of cells that participate in pursuit and cancellation in the flocculus. [23,24]

Within the last five years, examination of the ability to cancel the vestibulo-ocular reflex has become widespread in neuro-ophthalmological testing and adds a new dimension of diagnostic significance. It is now fairly common to find laboratories in which the vestibulo-ocular reflex, the pursuit system, and the optokinetic system can be stimulated in any combination, especially in ways that make these systems work against each other. Such testing procedures are already used in some clinics, and this is likely to increase.

RESEARCH NEEDS AND OPPORTUNITIES

Progress in oculomotor physiology is occurring at a phenomenal rate that is not likely to be matched by many other fields of bioscience. The use of improved tracer techniques and the ability to record neuronal activity in alert animals, separately or especially in combination, has opened the gates of research opportunity so wide that it will be some time before these techniques, even without refinements, will cease to provide valuable information. Not all the regions of the brain directly significant to oculomotility have been discovered. Some, only recently discovered, have not yet been explored by tracers to determine major efferent and afferent connections or have not been recorded from. These studies, of course, must also be done for new areas as they are discovered, so that all their cell types can be described quantitatively with respect to the movement of head, eye, visual objects, and attentional states.

Opportunities for Functional Analysis

The division of the oculomotor systems by function is not yet finished. There is still controversy, for example, about drawing sharp boundaries between the function and properties of the pursuit and optokinetic systems and determining whether it is possible to distinguish separate systems that create quick phases as opposed to saccades, fixation as opposed to pursuit, and cancellation of the vestibulo-ocular reflex as opposed to pursuit. These possibilities need to be explored. A system is distinguished as separate because of its different properties, such as eye movement type, gain, bandwidth, nature of the stimuli, and saturation limits; these properties must be discovered, described, and quantified. In addition to describing the properties of various subsystems, it would be desirable to design sensitive, clinical tests to detect abnormalities.

The influence of the otolith organs on eye movements, for example, is poorly understood and there are almost no tests for otolith function; the oculomotor system might provide a means for such

testing. The cervico-ocular reflex is also poorly understood in man. In general, laboratory scientists have studied horizontal eye movements most frequently, vertical movements occasionally, and torsional eye movement almost not at all. However, the clinician must deal equally with horizontal and vertical movements because disorders of either are common and have diagnostic significance. It would be desirable, then, to characterize oculomotor subsystems in all the dimensions in which they operate.

Stimulus factors to which the various subsystems respond need better definition. Most subsystems try to lessen the velocity of image motion on the retina, but the extent to which this is desirable has not been defined. If images move too slowly or too rapidly, visual ability decreases. What is optimal, however, is not known, nor how to define optimality because the visual system must perform a variety of tasks, such as identifying objects and judging their location and speed, and each may have a different, preferred range of retinal slip.[38] It is not certain how much of the visual world must move en bloc before the optokinetic, as opposed to the pursuit, system is stimulated. These are examples of dividing eye movements into subsystems by defining the visual circumstances for which each evolved.

The use of models will increase because they allow interpretation of the data and represent current ideas of how the oculomotor system works. This is especially important for abnormal eye movements; by providing an interpretation of the observed phenomena, models offer clinical insight into these conditions.

Opportunities with Techniques

The use of anatomical tracers and recording in alert animals certainly will continue to lead to major progress during the next five years, as new nuclei are discovered and explored and known nuclei are probed in finer detail. The current trend in techniques is toward methods that allow not only recording from a cell in an alert animal and knowing its behavior during various kinds of eye movements, but identifying its connections with other cells. This includes implanted electrodes for ortho- and antidromic stimulation, spike-triggered averaging and recording intracellularly so that the cell can be filled with dye and its processes studied histologically. Anatomical studies that reveal structure but not function, and recordings that reveal function without structure are still valuable and will continue to reveal important information, but techniques that allow study of both structure and function are obviously more valuable.

Other recently developed techniques may be expected to produce useful results in the future: kainic acid allows lesions to be made without interrupting fibers of passage; microstimulation in alert animals provides useful information because the currents used are localized; 2-deoxyglucose can measure brain regions metabolically active during certain types of eye movements.

It is, of course, impossible to predict future developments in techniques. If, for example, a transsynaptic tracer were developed, the rate and direction of progress in anatomy would change drastically. Other new techniques could not only alter how the oculomotor system is studied but which part or aspect of it is emphasized, as occurred when plasticity was first observed. Despite the unpredictable nature of basic research, a good rate of progress in knowledge of the oculomotor system may be expected in the next five years, whether or not new techniques are developed.

Opportunities by Anatomical Area

In the orbit, the special function of multi-innervated slow muscle fibers is not known, nor is the function of muscle proprioception or how hysteresis in the muscle is taken into account by central commands. In the motor nuclei, nothing is known of the function of the axon collaterals of the motoneurons or the purpose of the interneurons in the oculomotor nucleus. In the vestibular nucleus, investigators have a fair picture of the different classes of cells and the signals they carry, but still cannot incorporate them into an overall scheme because, to a large extent, their anatomical interconnections are not known. The vestibular nuclei, prepositus nuclei, abducens nuclei and surrounding pontine and medullary reticular formations are contiguous and probably form an area in which horizontal eye movements, particularly the vestibulo-ocular reflex, are organized. Deducing the operation of these circuits would constitute a major advance in oculomotor physiology.

New discoveries in the mesencephalon around the oculomotor nuclei[17] have focused attention on the organization of vertical eye movements, but this research has only raised more specific questions, among which are: What are the relative roles of the medial longitudinal fasciculus and brachial pathways in subserving the vertical vestibulo-ocular reflex? Which cell types in the interstitial nucleus of Cajal project to or receive signals from the vestibular nuclei? Do vertically acting, saccade-related neurons project directly to vertically-acting motoneurons? In what planes do the neurons in this region act relative to the planes of action of the vertically-acting muscles? These are only a few of many such questions that must be answered to understand vertical and torsional movements.

Although progress in understanding the oculomotor role of the cerebellum has been remarkable in the last few years, specific questions remain. In

general, investigators know that an important role of the flocculus is to decrease retinal image velocity in a variety of situations that would otherwise cause it, such as during pursuit, optokinetic movements, fixation, vestibular movements, and just after saccade. In subprimates, the retinal image slip signal projects from the retina by way of the accessory optic system to the flocculus by both a mossy fiber and climbing fiber pathway, but these pathways remain unexplored in primates. Moreover, investigators have no good hypotheses as to how this signal is converted in the flocculus to generate the oculomotor commands for decreasing retinal slip; nor do they know the specific projection sites of the Purkinje cells mediating these commands. Other oculomotor areas of the cerebellum, notably the vermis around lobes V-VII and the deep cerebellar nuclei, remain relatively unexplored. Nor is it known how the signals observed on the Purkinje cells of these areas reach their oculomotor targets in the brainstem or what the purpose is of these signals.

So far, research in the superior colliculi suffers from the dichotomy, imposed by techniques, between knowledge of structure and knowledge of function. The most interesting oculomotor cells are those in the deep and intermediate layers that discharge in relation to saccades. To where do these cells project? To deduce the sequence of events that lead to a saccade, a cell's saccadic behavior must be related to the target cells to which it sends its signals and, in turn, to their behavior. Conversely, where do the signals, such as the saccadic burst seen on these cells, come from? Some of these cells also reflect the animal's intention to make a saccade to a certain target. Where does this signal come from? These questions are much harder to answer because the deep layers of the colliculus receive inputs from many regions. The anatomical relationships between functionally identified cells must be established since the information that can be obtained by simply recording from alert animals is limited. The locations of targets in visual space are coded on the colliculus according to the retinotopic map, yet there is growing evidence (Figure 2) that saccadic commands are issued in a head or spatial coordinate system.[39] Thus, these studies address the fundamental issue of how the locations of targets in space are perceived and how motor commands that interact with them are issued.

Similar considerations apply to areas rostral to the mesencephalon. In the thalamus and cerebral cortex, behavior reflects less the details of the desired eye movement and more the intentions of the animal. The problem is well illustrated in the frontal eye fields, where many cells fail to discharge during saccades when a monkey looks around a familiar laboratory, but they do so if the target is in some sense "interesting." These areas are clearly involved with cognitive processing. For this reason, results are much more difficult to interpret, and much new knowledge is needed before hypotheses can be proposed for how this processing is done. Here, too, as in the colliculus, it will become increasingly desirable to know something about the axonal projections of cells that have been identified functionally on the basis of their discharge behavior.

Opportunities Involving Neurotransmitters

The cure of periodic alternating nystagmus by baclofen has drawn attention to the possibility of using other drugs that act on neural transmitters to assist in other oculomotor disorders. Progress in this area probably must await the development of new drugs. The effect of transmitter-like drugs on eye movements in alert animals has not, however, been examined quantitatively; such examination could provide important clues. It would also be helpful to increase knowledge of the transmitters used in various parts of the oculomotor system.

Opportunities in Plasticity

In addition to the seven known types of oculomotor plasticity, it would be useful for two reasons to discover all the forms of plastic adjustment of which the oculomotor subsystems are capable. One reason is to emphasize further that in motor physiology in general, adaptive mechanisms abound and exist to eliminate dysmetria in all forms of movement control. The other is the hope of finding some form of plasticity that could be utilized in the clinic to counteract some aspect of an eye movement or vestibular disorder. It is important to continue trying to reveal the neural mechanisms of all forms of plasticity, although at present the system most amenable to further study seems to be the vestibulo-ocular reflex because it is the simplest and more is known about its neural substrate. It has been shown that the flocculus and its climbing fiber system are essential to this plasticity, but its key elements, presumed to be modifiable synapses, have not been located. Before the role of the climbing fibers in plasticity can be determined, it is essential to learn much more about the nature of climbing fiber action on Purkinje cells.

On the efferent side is the problem of how the gain is actually altered by the modulation of Purkinje cell discharge rate. This modulation changes in appropriate ways when the gain is changed, although this change is not reflected in the vestibular nucleus in the monkey and only inadequately in the cat. Nor is it understood how learned commands get from the flocculus to the motoneurons. If, through research in this area, the mechanism of at least one form of motor learning

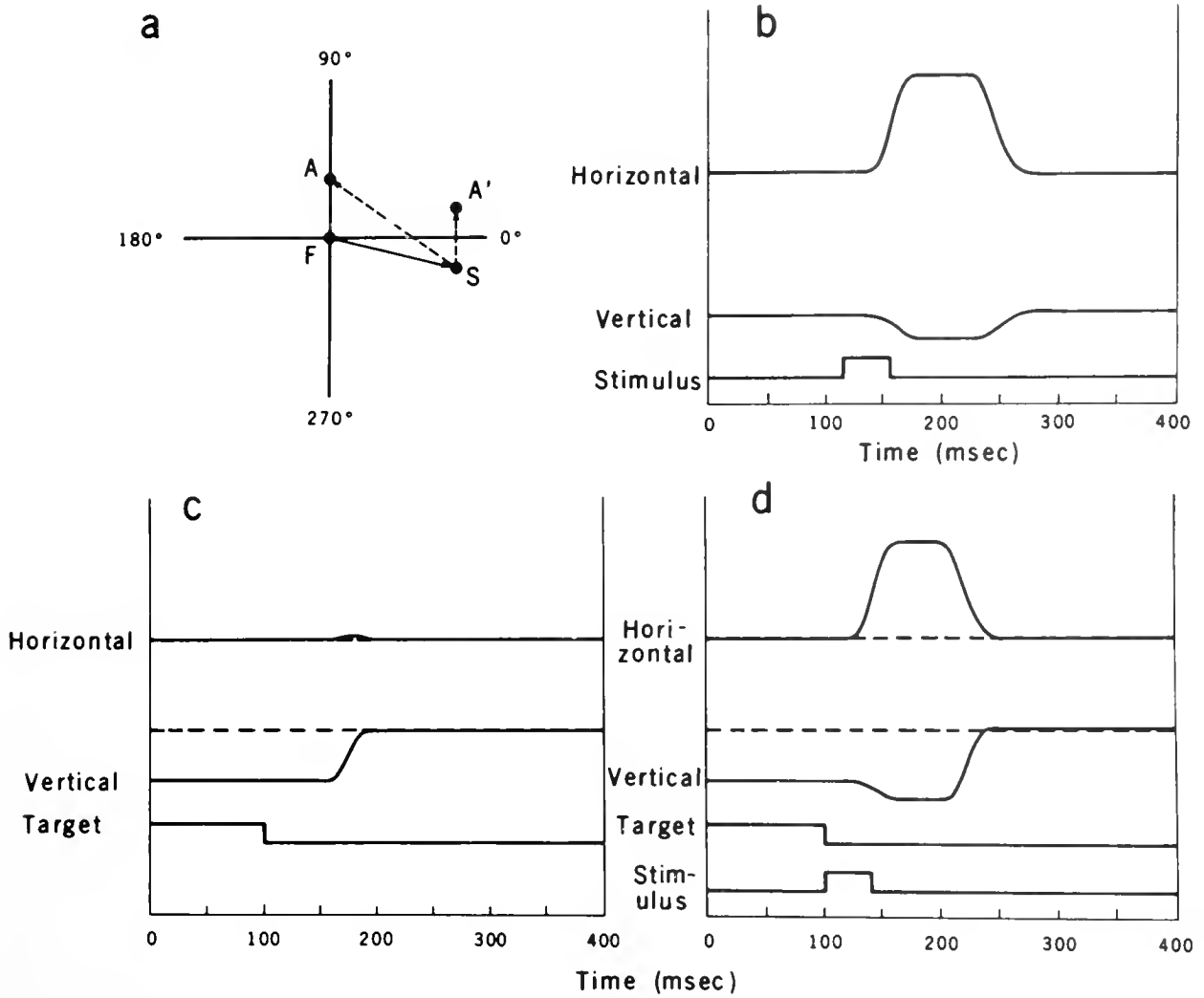

FIGURE 2. Evidence that saccades are not planned in a retinotopic reference frame. In (a) a monkey is trained to fixate a central target at F. If the left superior colliculus is electrically stimulated, a saccade is evoked to point S. The time course of the saccade is shown in (b). In (c) a target is flashed briefly (100 msec) at point A and the monkey is trained to make a saccade to it. In (d) both events occur at once; the colliculus is stimulated while the monkey is planning to saccade to A. If the planned saccade were coded retinotopically, it would take the eye to A′. But the movement to S was taken into account by the saccadic mechanism, and the monkey saccaded correctly from S to A even though no retinal error signal existed corresponding to this saccade. (Figure courtesy of D. A. Robinson.)

could be located and described, it would have broad implications throughout all of neuroscience.

Opportunities for Research in Lower Animals

While the alert primate will doubtlessly continue to be the main experimental model for studies of oculomotility, other animals also offer interesting opportunities for study. The cat and rabbit already figure heavily in oculomotor research, but even nonmammalian species may provide experimentally useful features. A major advantage of lower species is simplicity.

A complication of primate oculomotility has been the interaction of seemingly separate subsystems such as the pursuit and optokinetic systems and the vestibulo-ocular reflex. Afoveate vertebrates (mammals and nonmammals), which lack a pursuit system, would seem to be logical candidates for studies of optokinetic and vestibulo-ocular systems without the intrusion of pursuit. Another advantage of simpler animals is the relatively small number of neurons involved, many of which have a clearer and narrower range of functions than the more numerous, multipurpose neurons of many primate subsystems. Examples are the "object" and "field" neurons in certain insect brains. The insects are faced with the same visual problem as humans, namely, how to attend to an object moving with respect to the stationary field. In certain insects, specialized interneurons are activated by movement of either "object" or "field" and they presumably control the

animal's pursuit behavior. It would be of general interest to know the neural network underlying this common visual operation.

Simpler animals often provide certain technical advantages. The brain of a fish, for instance, is mechanically extremely stable, mainly because there are no vascular pulsations. (Fish have a single-loop circulatory system, and most of the cardiac pressure and pulse are lost in traversing the first bed of capillaries in the gills.) Thus, central neurons that have been impaled by a microelectrode can be held a long time. This facilitates injection of intracellular markers, such as horseradish peroxidase. Nonprimates also are relatively inexpensive. When a fundamental process (such as plasticity, whether in the oculomotor system or elsewhere) is to be studied, it makes sense to study it first in a system in which the research can be done quickly and cheaply. This is particularly important for studies of the oculomotor system, in view of the endangered status of macaque monkeys and the low yield (one or two cells per animal) of the intracellular marking techniques.

Finally, the systems-analytic approach to neural function described in the section on Recent Accomplishments emphasizes that control systems are goal-directed. For instance, if the goal of a system is to reduce retinal slip, then it is likely that analogous systems in different species use some of the same stratagems. A deeper understanding of oculomotor control in nonprimates should clarify and strengthen understanding of the human oculomotor system. A broader approach to the study of oculomotion should be encouraged.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Conjugate Eye Movements," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base includes areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort. Nonetheless, additional applications for research grants in these areas may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Base

- Study the anatomy and operation of the circuits in the mesencephalon, pons, and medulla, near the motor nuclei of the extraocular muscles, and their connections with the vestibular nuclei, that mediate the horizontal, vertical, and torsional vestibulo-ocular reflex and act as a final output stage for all other types of horizontal, vertical, and torsional conjugate eye movements.
- Study the anatomy and operation of the circuits through which the cerebellum acts to influence all types of eye movements.
- Identify and characterize all of the oculomotor subsystems. Determine the appropriate stimuli for each, the metrics of the response in the normal population, and the importance of each in vision and perception. The interactions between these subsystems need study and the neuronal substrate of these interactions should be investigated in animals using a variety of stimulus modalities.
- Study the role of higher centers, such as the superior colliculus, thalamus, and cerebral cortex in creating eye movements. Especially important would be techniques that allow association of the cell's behavior during various visual stimuli, oculomotor responses, and mental states with the cell's afferent connections and axonal projections.

Program Development Priorities

- Discover and characterize all types of sensorimotor plasticity in the oculomotor system, and study the neural mechanisms involved and the part played by the cerebellum.
- Develop working hypotheses to explain human eye movement disorders. One approach may be to develop a hypothetical system or model that best describes normal data and, when suitably modified, describes the abnormal movements. Whenever possible, knowledge gained in the laboratory should be applied by this or any other method to clinical problems. Important to this

process is a quantitative description of the abnormal movements.

- Study the influence of drugs that affect neural transmitters on the various parts of the oculomotor subsystems in normal humans and animals. As new drugs become available, their effect on oculomotor abnormalities should be studied. The neural transmitters in the oculomotor system should be identified.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

OCULAR MOTILITY AND STRABISMUS

Structure and Function

CONJUGATE EYE MOVEMENTS

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Base			
A. Study the anatomy and operation of mesencephalic and pontine circuits involved in conjugate eye movements.	16	1	17
B. Study the circuits through which the cerebellum influences eye movements.	2	1	3
C. Identify and characterize all oculomotor subsystems and their interactions.	9	0	9
D. Study the role of higher brain centers in creating eye movements.	8	0	8
Program Development Priorities			
A. Discover and characterize all types of sensorimotor plasticity in the oculomotor system: neural mechanisms and role of cerebellum.	2	1	3
B. Develop hypotheses to explain eye movement disorders: relate hypothetical system or model to clinical problems.	2	1	3
C. Study the influence of drugs on neurotransmitters in oculomotor subsystems.	0	2	2
Subtotal Grants	**39**	**6**	**45**
(% of Program)	**(15)**	**(7)**	**(13)**
Total Estimated Cost	**$3,277,000**	**$1,133,000**	**$4,410,000**

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7

VERGENCE AND ACCOMMODATION

INTRODUCTION

PERSONS WITH NORMAL binocular vision respond to near objects of interest by converging their eyes to position images on the two foveas and increasing accommodation of the crystalline lens to provide sharp retinal images. These vergence and accommodation functions are highly interactive and have enormous survival value, not only for recognizing oncoming objects that might be harmful, but for sustained activities such as reading.

In some persons, accurate convergence and accommodation cannot be achieved simultaneously: only one function is achieved at the expense of the other, creating either a single blurred image or clear but double vision (strabismus). If a child with significant uncorrected farsightedness accommodates fully to overcome the refractive error, the associated accommodative convergence will cause the eyes to overconverge, resulting in esotropia with several sensory deficits. Alternatively, the farsighted child may attempt to keep the eyes straight by *not* accommodating, in which case the blurred imagery at all viewing distances can potentiate development of sensory deficits, particularly when the refractive errors are unequal. Either response to such vergence-accommodation discordance leads to sensory abnormalities, such as suppression, loss of stereoscopic depth, and amblyopia. Clearly, strabismus is much more than a cosmetic deficit.

Although there are known genetic precursors to strabismus, its etiology is unknown. Increased knowledge of how the neonate develops the power of visual accommodation and why the child achieves either clear or double vision will result in better understanding of the genesis of strabismus and ultimately improved prevention and treatment.

Knowledge of the underlying structures and function of the vergence and accommodation systems, separately and in combination, is important for understanding how these systems operate under normal and abnormal conditions.

Significant deficits in the vergence system may affect as many as 25 percent of the general population; thus, these anomalies rival the prevalence of refractive errors. Some 15 percent have symptom-producing heterophorias, about 5 percent have strabismus, and another 5 percent have fusional vergence anomalies. The associated symptoms include asthenopia, diplopia, suppression, amblyopia, and loss of stereoscopic depth perception.

Although accommodative anomalies are uncommon, or at least not commonly recognized among the young, they are virtually universal among the elderly, in whom crystalline lens sclerosis and ciliary body vascular changes lead inevitably to presbyopia. As a result, most persons over 50 reduce their nearpoint tasks, remove their myopia-correcting glasses for near work, or wear bifocals or reading glasses.

Corrective lenses for presbyopia are fairly effective in providing clear vision at close distances, with minimal restriction in work activities. However, the presbyope's poor contrast sensitivity persists, especially for low spatial frequencies, and probably accounts in large measure for the visual limitations of older persons who have an otherwise intact visual system. The time, effort, and money invested in managing disorders of vergence and or accommodation is enormous, probably incalculable, and certainly at present unknown.

The major neural and muscular components that mediate accommodation have been known in broad outline for a long time, but the advancement of knowledge in this area has not kept pace with the enormous progress being made in neurophysiology.

However, the results of neurophysiological research are helping in reevaluating old tenets. For example, it had long been thought that the parasympathetic pathway to the ciliary body shares with the innervation of the iris sphincter the property of synapsing in the ciliary ganglion. Recent experiments [1] with monkeys suggest a direct pathway to the ciliary muscle. The results might lead to a theoretical framework or mechanism by which higher neural centers could evoke relatively permanent peripheral changes such as refractive myopia. For both accommodation and vergence, very little is known about the detailed events between the retinal neural signal and the final commands to the ocular muscles, in contrast to the burgeoning knowledge of the saccadic system (see Chapter 6, "Conjugate Eye Movements").

Recent-onset deficits in vergence and/or accommodation can play a key role in isolating brain lesions (see Chapter 9, "Motor Neuro-Ophthalmic Disorders").

Knowledge of the stimuli for vergence and accommodation in the human adult is fairly complete, and knowledge of the basic response characteristics of vergence and accommodation is developing. However, essential structural and functional details are still needed, especially to explain how accommodation and vergence work when the head and body are free to move.

SUBPROGRAM OBJECTIVES

- To learn which features of numerous stimuli (both visual and nonvisual) are responsible for the specific responses of vergence and accommodation.
- To extend knowledge about the response characteristics of vergence and accommodation for the stationary head and body to situations where both are in motion.
- To explore the interactions between vergence and accommodation, especially in terms of plasticity in relation to normal development and aging.
- To develop animal research programs designed to clarify the underlying neurophysiology of accommodation and vergence.

OVERVIEW OF CURRENT RESEARCH SUPPORT

In FY 1981, the National Eye Institute supported six research projects at a total cost of $384,000, which involved the study of vergence and accommodation. Other agencies, components of the Department of Health and Human Services other than the NEI, the National Science Foundation, and the Department of Defense support research relating to eye movements. None of the research projects supported by these agencies is specific to vergence or accommodation, but several deal with coordination of eye movements with movements of the head, hands, and body.

RECENT ACCOMPLISHMENTS

The 1893 classification of Maddox [2] is the basis for current understanding and investigation of vergence eye movements. Tonic vergence was proposed as the component that moves the eyes from some unknown anatomical position of rest to a more convergent position, which is usually specified relative to a designated point in space. Any deficit (exophoria) or excess (esophoria) of tonic vergence is compensated by another component, reflex or fusional vergence, which is stimulated by retinal image disparity (disparity vergence [3]) and constant use (conditioned vergence [4]). The vergence that results directly from accommodation, or more accurately from accommodative effort, was called accommodative convergence. The amount of convergence resulting from each diopter of accommodation was represented as the ratio of accommodative vergence to accommodation (the AC/A ratio). The fourth vergence component proposed by Maddox is that due to knowledge of nearness and was called psychic or proximal vergence.

The Maddox analysis was refined by Percival [5] and Sheart [6] and greatly advanced through separate investigations by Fry, [7,8] Hoffstetter, [9] and Morgan [10,11] who indicated the value of (1) visualizing the interrelationships among the convergence components when all are plotted in a single graph, (2) using such a graphical display for analysis of clinical data, (3) distinguishing between stimulus and response data, particularly when studying accommodative vergence, and (4) dealing with the vergence components as fundamental, perhaps neurologically independent, variables.

Tonic vergence (phoria) appears to be somewhat dynamic but basically stable with time [12] and age. [13]

Accommodative vergence, while initially believed to be linearly related to accommodation [9] and to be stable, [14,15] has since been shown to be curvilinear [16] and subject to at least short-term change by training fusional vergence, [17,18] increasing the lens power for undercorrected myopes, [4] and optically widening the interpupillary distance. [19] Accommodative convergence has been demonstrated in human infants as young as two months of age. [20]

Positive fusional vergence seems to be rapidly alterable by vision training, including visual [18] and auditory feedback, [21] but negative and vertical fusional vergence, along with cyclofusional movements, seem to be capable of smaller and slower changes. Of importance is the finding of characteristic incomplete cyclofusional movements associated with rotary sensorial shifts, [22] indicating changes in retinal correspondence. Marked stability of retinal correspondence is nearly always present during vergence responses by persons with normal correspondence. [23,24] Cyclofusional changes at a sensory level are reminiscent of the changes in retinal correspondence with changes in tonic and fusional vergence in squinters with anomalous correspondence. [25,26]

Proximal vergence is influenced by the perceived distance of objects, and it can be affected by the size of objects through the mechanism of size constancy. [27–29] Related to this effect is the finding that perceived distance in dim light is biased towards an intermediate value that is correlated with the physiological resting state of convergence and is independent of that for accommodation, [30] even though both can provide usable cues to perceived depth for near distances (within a meter). [31]

Although vergence (disjunctive) and conjugate eye movements are organized independently, [32] they normally interact in oculomotor tracking. [33] Of even greater importance is the question of how such ocular movements are coordinated with head and body movements. Under such dynamic conditions, the eyes adjust with seemingly controlled imperfection designed to prevent image stabilization and perceptual fading; [34] in spite of large vergence errors, vision is fused, [35] suggesting functional enlargement of Panum's fusional areas. This interpretation is consistent with that obtained in an earlier study. [36]

Fusional (disparity) vergence is initiated by disparate images even when the shapes are different in the two eyes. [37] Completion of these eye movements, however, seems to require similar image shapes and involve a process of shape selection. [38] By concentrating only on initiating vergence movements, investigators have recently demonstrated that squinters with anomalous correspondence respond, albeit slowly, to disparate stimuli with respect to (1) the fovea of the preferred eye and (2) the displaced directional reference point in the deviating eye. [39] After many minutes, vergence movements in such persons can be completed [40] and then maintained by a "slow neural integrator," [41] which may be present in nonsquinters and relate to their adaptation to prisms. [42]

The irregular fusional vergence movements of squinters with anomalous correspondence have been attributed in part to their irregular distribution of corresponding retinal points. [43] Further, it has recently been reported [43] that when intermittent exotropes have their eyes "straight," the horopter has such marked concave curvature toward the eyes (a negative Hering-Hillebrand deviation) that objects located only a few degrees peripheral to a singly seen central target will fall on disparate retinal elements; a small divergence of the eyes activated to reduce the peripheral image disparity might continue unabated and result in a frank exotropia. Indeed, understanding disparity vergence, particularly in squinters, may require knowing a subject's distribution of corresponding retinal points, since it is the stimulation of disparate (noncorresponding) retinal points that ordinarily produces fusional vergence movements. Furthermore, esotropic amblyopic eyes have significant monocular spatial distortions [44] that not only account for much of the amblyopic eye's behavior but, when added to the space values of the preferred eye, might account for the irregular distribution of corresponding retinal points (horopter) and vergence movements of these subjects.

The retinal image disparities responsible for fusional vergence movements are also responsible for stereoscopic depth perception. Normally, the eyes adopt a vergence posture that more or less minimizes the disparities across the retina. Within this vergence posture framework, stereoscopic depth is normally produced by localized regions of disparity. An attractive stereopsis theory [45] proposes that disparities of different magnitudes are processed independently by differently tuned spatial frequency channels. Large disparities are presumably dealt with by low spatial frequency units; these produce vergence which brings into correspondence high spatial frequency channels dealing with small disparities. A recent study [46] showed that relatively high spatial frequencies can initiate rapid vergence shifts for disparities as large as about plus or minus one-half degree. To test the theory fully, one needs to use high spatial frequency targets with large disparities, such as would be involved in shifting binocular fixation from a remote target to a near one.

Retinal image disparities large enough to produce coarse stereopsis and initiate vergence movements when briefly presented to most people lead sometimes to reduced or absent vergence movements of either the convergent or divergent type; all such persons exhibit a similar (crossed or uncrossed disparity) type of stereoanomaly. [47] Because not all

stereoanomalous persons exhibit a parallel vergence anomaly, one can conclude that coarse disparity information is processed for vergence movements before stereopsis.

Fixation disparity, the small error of exact bifoveal fixation, has been developed fairly thoroughly on a theoretical and clinical basis by Ogle.[23] New interpretations of fixation disparity have improved the general understanding of the vergence system. Fixation disparity is described[48] as a steady-state error of the neural integrator controlling fusional vergence. The amplitude of fixation disparity is inversely related to adaptation of the phoria to prism; this is a phenomenon of the slow neural integrator.

Ogle[23] measured fixation disparity with various added lens powers to determine AC/A ratios under binocular fused conditions; these ratios differed considerably from those obtained more conventionally by measuring the vergence position of the covered eye while accommodative stimuli were presented to the fixating eye. This difference in measured AC/A ratios suggested a difference between monocular and binocular blur-driven vergence. Further evidence for this intriguing notion has recently been offered[49] that suggests a possible modification of the classical Maddox classification. The new interpretation is that an independent convergence accommodation mechanism exists, which influences control through accommodative feedback.[50]

In a classification of accommodation that parallels the Maddox classification of vergence, Heath[51] has proposed tonic, reflex, convergence, and proximal components of accommodation. Tonic accommodation recently has been addressed[30] in research on night myopia, empty-field myopia, and instrument myopia, all of which seem to relate to a dark focus or resting position of accommodation that is unique for each person. (To the extent that the dark focus represents a neurally induced change in crystalline lens curvature, there is no associated change in "accommodative vergence.")[52] Reflex accommodation has long been believed to result from vergence of light at the retina; however, other factors such as chromatic aberration also seem to be likely stimuli.[53] Indeed, it has been shown[54] that any perceptible cue that reveals the direction of movement of a target is sufficient to permit correct accommodative responses; no single cue or particular combination of cues is necessary.

Convergence accommodation defied experimental confirmation for many years until Fincham[55] and Morgan[56] successfully opened the accommodative loop by creating a very large depth of focus. The resulting convergence accommodation/ convergence ration (CA/C) decreases regularly with increasing age, being about 0.2D/1 for 40-year-olds.[57] Such a result is consistent with a decrease in lens capsule plasticity with age. Not so easily explained is the fairly constant AC/A ratio with age.[13] (As mentioned earlier, the AC/A ratio is readily changed on a short-term basis.)[4,17,19] Proximal accommodation has been difficult to exhibit unequivocally because the accommodative changes seem to result from effects of proximal vergence on accommodation.[28]

Major differences in the two eyes' amplitude and form of accommodative response have been reported in a normal subject.[58] It is interesting to speculate whether such differences in accommodative dynamics might indicate the time of onset of presbyopia and, further, whether accommodative dynamics might be improved by appropriate use of visual and/or auditory feedback. If eccentric and unsteady fixation of amblyopic eyes[59] and the large and rapid ocular oscillations of persons with congenital nystagmus[60] can be improved by providing auditory feedback of eye position information, it seems reasonable that auditory or other feedback cues might be useful in extending the amplitude of accommodation in pre-presbyopes and perhaps delay the onset of presbyopia. The converse of this effect, namely relaxation of accommodation, recently has been reported[61] for a patient whose myopia was reduced while using feedback. Further, it has been found[54] that young subjects given tones whose pitches were randomly selected made accommodative responses indistinguishable in latency and accuracy from those normally elicited by random shifts in real target position.

The recent finding[62] of optimal performance for both accommodation and contrast sensitivity at spatial frequencies of 3–5 cycle per degree suggests that contrast sensitivity may be objectively assessed by monitoring accommodative responses. Indeed, objective methods such as preferential looking and visually evoked potentials have been used to assess development of acuity and contrast sensitivity of human infants during the first six months of life. Photorefraction, a relatively new technique for measuring the accuracy of accommodation of human infants, shows that many newborn and one-month-old infants exhibit inconsistent fluctuations of accommodation over the full range, and that accurate accommodation for most distances does not occur until about three months.[63]

RESEARCH NEEDS AND OPPORTUNITIES

The complexity of the vergence system and its component interactions, as well as interactions with accommodation, versions, and the vestibular system,

makes research in this area difficult. Nonetheless, steady progress has been made, and with encouragement provided by future NEI grant support, major advances are expected in basic and clinical research relating to vergence and accommodation. This area of research has been designated in this Plan as one that should be expanded through additional support by the National Eye Institute.

The wide range of human disorders of vergence and accommodation should be further examined, as these studies will help explain many aspects of normal mechanisms. The technology is at hand for simultaneous objective measurements of accommodation and vergence in situations where the head and body are free to move. Such global and interactive research will surely yield valuable information, but other less expensive investigations are needed also. Laboratory research must take into account the problem of individually manipulating vergence or accommodative functions that may produce false impressions of how the functions operate and interact in normal life.

The development of accommodation and convergence in the human neonate is clearly an area of research opportunity that needs to be pursued. Studying plasticity in these systems and the influence of perturbations should lead to understanding of the mechanisms underlying strabismus.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Vergence and Accommodation," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base consists of an area of ongoing research in which the current level of activity is considered adequate. Nonetheless, additional research grants in this area may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Base

- Study the innervation of the ciliary muscle relative to pathways, synaptic mechanisms, and possible transneural trophic influences.

Program Development Priorities

- Define in detail the adequate accommodative and vergence stimuli for the neonate and characterize the developing associated motor responses.
- Elucidate the accommodative/vergence relationships in the neonate and ascertain the critical period for influencing this synkinesis.
- Explore and define the interactions and plasticity of the interactions between vergence and accommodation in the normal developing neonate (human and primate) and in neonates with a predilection for strabismus.
- Explain the mechanisms responsible for (1) plasticity of anomalous retinal correspondence associated with certain but not all vergence movements, and (2) the relative rigidity of normal correspondence in strabismics and nonstrabismics.
- Study the basic anatomy, physiology, and behavior in the vergence and accommodation systems in appropriate animal models.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

OCULAR MOTILITY AND STRABISMIS

Structure and Function

VERGENCE AND ACCOMMODATION

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Base			
A. Study the innervation of ciliary muscle.	0	1	1
Program Development Priorities			
A. Define accommodative/vergence stimuli for neonate; characterize developing associated motor responses.	1	1	2
B. Elucidate the accommodative/vergence relationships and the critical period for influencing them in the neonate.	0	2	2
C. Explore and define interactions/plasticity of vergence/accommodation in neonates: normal and those with predilection for strabismus.	1	1	2
D. Explain plasticity of anomalous retinal correspondence with some vergence movements, and rigidity of normal correspondence in strabismics and nonstrabismics.	1	1	2
E. Study the anatomy, physiology, and behavior in vergence and accommodation systems in animal models.	3	1	4
Subtotal Grants	**6**	**7**	**13**
(% of Program)	**(2)**	**(8)**	**(4)**
Total Estimated Cost	**$384,000**	**$890,000**	**$1,274,000**

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8

MUSCLE STRUCTURE AND PHYSIOLOGY

INTRODUCTION

THE EXTRAOCULAR MUSCLES effect both conjugate and vergence eye movements as well as eye position. Because of the central role of the extraocular muscles in all types of eye movements and the interdisciplinary nature of research in muscle structure and physiology, no separate discussion of this topic is included in this report. Because most research on muscle structure and physiology is focused on some particular aspect of ocular motility or function, discussion of this subject is included in the other chapters in this section on Ocular Motility and Strabismus.

Listed below, however, are Subprogram Objectives and Program Development Priorities for those aspects of research on muscle structure and physiology that are not specifically related to any of the other aspects of Ocular Motility and Strabismus.

SUBPROGRAM OBJECTIVES

- To understand the structural characteristics and functioning of the extraocular muscles.
- To understand the involvement of other ocular muscle systems in processing visual information.

OVERVIEW OF CURRENT RESEARCH SUPPORT

Only four research projects, at a total cost of $347,000, were funded in FY 1981 in this subprogram. These projects were basic studies to explore the structural and functional properties of particular types of extraocular muscles. However, other research projects supported by the NEI include studies of muscle structure and physiology that relate to specific types of eye movements, to development, or to strabismus or oculomotor disorders. These projects are included in the subprograms dealing with the latter topics.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Muscle Structure and Physiology," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have all been designated as Program Development Priorities and include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Development Priorities

- Determine the molecular and cellular properties of extraocular muscles and their organization and function in normal and pathological conditions.

- Study the properties of other muscles or muscle systems that directly affect the visual process.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

OCULAR MOTILITY AND STRABISMUS

Structure and Function

MUSCLE STRUCTURE AND PHYSIOLOGY

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Development Priorities			
A. Determine the molecular and cellular properties of extraocular muscles; organization and function in normal and pathological conditions.	3	1	4
B. Study the properties of other muscles or muscle systems that directly affect the visual process.	1	1	2
Subtotal Grants	**4**	**2**	**6**
(% of Program)	**(1)**	**(2)**	**(2)**
Total Estimated Cost	**$347,000**	**$241,000**	**$588,000**

9

STRABISMUS

INTRODUCTION

STRABISMUS IS A misalignment of the two eyes; that is, the fovea of one eye is not aligned with the same object in space as the fovea of the other eye. This misalignment of the visual axis can be horizontal (esotropia, exotropia), vertical (hypertropia, hypotropia), or torsional (incyclotorsion, excyclotorsion). Research into the etiology, improved diagnosis, and management of strabismus is a major concern of the National Eye Institute.

It is estimated that at least 3 to 4 percent of the population is born with or develops strabismus during the first six years of life. In a 1971–1972 national survey, an estimated 19.5 percent of the civilian, noninstitutionalized United States population, ages 1–74, were found to have a manifest or latent eye muscle imbalance.[1] Mainfest strabismus or tropia was found in 3.7 percent of the population; 1.2 percent had esotropia, 2.1 percent had exotropia, and 0.6 percent had hypertropia. Among children 1–3 year of age, 1.9 percent were found to have tropia.[1]

The cost of remedial care is substantial both for inpatients, including hospitalization, anesthesia, and surgery, and outpatients, including office visits, eyedrops, glasses, bifocals, prisms, occluders, and orthoptics.

Strabismus is not just a cosmetic problem, it also creates lifelong functional difficulties. In many forms of human strabismus, amblyopia is an associated problem (see Chapter 3, "Amblyopia"). In addition, esotropic patients have their binocular visual field restricted and lose normal binocular function (central and peripheral fusion). These problems create job handicaps, especially in certain occupations that require fine, manipulative, binocular skills which these patients do not have.

The annual number of surgical operations for strabismus is second only to that for cataract extraction, which is the most common form of ophthalmic surgery. Eye muscle operations represent 11 percent of all eye surgery.[2] In 1976, 996,000 office visits to physicians were made for strabismus by patients of all ages; 563,000 of these visits were made by patients under age 15, representing about 13 percent of all visits for eye care in this age group.[2]

The etiology of some forms of strabismus is understood. The role of accommodation and hyperopia in the genesis of accommodative esotropia has been known since Donders described this relationship.[3] Some forms of strabismus have been recognized to be secondary to extraocular muscle palsies or are associated with thyroid eye disease or orbital floor fracture. Little is understood about the etiology of early infantile (congenital) strabismus, a common form. In addition, the strabismus associated with certain neuro-ophthalmic diseases is still poorly understood. Strabismus is a symptom of a neurologic disorder. The major public health problem of strabismus is in its management, and the greatest chance of public benefit lies in support of research in which management strategies are emphasized. Although we have some empirical knowledge about surgical treatment of human strabismus, understanding of eye movement mechanics and central innervational input remains limited.

Amblyopia, a major problem that occurs frequently in association with human strabismus, is itself a public health problem because the visual loss it causes may be permanent and render the patient essentially monocular with no possibility of achieving normal binocular function. Should the normal eye suffer visual loss later in life due to trauma, degenerative disease, or some other cause, the patient may become functionally blind.

The systemic disorders often associated with human strabismus include thyroid disease, diabetes, head trauma as well as direct eye trauma, neurolo-

gic disorders including myasthenia gravis, progressive external ophthalmoplegia, and multiple sclerosis, and in more unusual instances, certain viral diseases such as herpes zoster. In addition, certain congenital disorders can be associated with strabismus, such as Moebius syndrome, congenital absence of an extraocular muscle, Brown's syndrome, and Duane's syndrome.

SUBPROGRAM OBJECTIVES

- To learn more about the natural history and epidemiology of human strabismus and devise cost-effective methods for its early recognition.
- To improve methods of measuring strabismus, particularly in young or uncooperative patients, and of evaluating ocular rotations.
- To devise new methods for the study of noncomitant strabismus, including the differentiation of innervational and mechanical causes.
- To improve methods of nonsurgical treatment of strabismus including optical, pharmacological, and orthoptic techniques.
- To refine the surgical approaches to strabismus therapy.
- To develop strategies that create and promote stability of the therapeutic result.

OVERVIEW OF CURRENT RESEARCH SUPPORT

The National Eye Institute supported only nine projects dealing with strabismus totalling $618,000, of a total of 268 grants funded in the Strabismus, Amblyopia, and Visual Processing program in FY 1981.

A few of the projects combined strabismus and amblyopia research. The NEI-supported investigations of strabismus included studies on: (1) the clinical implications of vergence anomaly, (2) the intraocular transfer of after-effects in strabismus, (3) depolarizing nicotinic antagonists and eye positions, and (4) clinical recording of human saccades to aid in diagnosing certain disease states.

Several new strategies may be useful in increasing support for research on this significant public health problem. The name change for the NEI program in which strabismus research is classified from Sensory and Motor Disorders of Vision to Strabismus, Amblyopia, and Visual Processing is an excellent first step. New methods must now be found to encourage the submission to the NEI of quality proposals for research on human strabismus.

RECENT ACCOMPLISHMENTS

Eye Movements

Saccadic velocity eye movement testing has been useful diagnostically in differentiating between paretic and restrictive disorders of ocular motility.[4–6] These tests have also been used to help diagnose various neurological diseases with eye movement abnormalities.

Surgery

Studies of the delineation of surgical planes, fascia, and extraocular muscle anatomy have been helpful in performing complication-free strabismus surgery.[7] Also, new approaches to oblique muscle surgery have improved results.[8,9]

Computer techniques, based upon both eye movement modeling theory and the results of previous strabismus surgery, have been applied to assist in surgical decision-making.[10–12] Some of this work has been done with intermittent exotropia.

New suture materials and needles specifically designed for strabismus surgery have been developed.[13] The use of the posterior fixation suture (Faden technique) has been described for certain types of strabismus[14] (dissociated vertical divergence, esotropia with a high AC/A ratio). With this technique, the muscle is tacked down to the sclera posteriorly (with or without recessing its insertion) to provide a more substantial weakening effect from surgery.

Adjustable suture techniques have been described in which the postoperative ocular position and rotations can be changed within the first few days after surgery.[15,16] Adjustment procedures have been developed for strengthening as well as weakening extraocular muscles following strabismus surgery. The use of an adjustable suture in oblique muscle surgery has also been reported.[17]

The spring-back balance test, for use during surgery, provides a new way of assessing mechanical muscle and orbital factors.[18] The goal of this test is to provide a more accurate balance of forces and alignment postoperatively.

More aggressive strabismus surgery has been performed to correct some problems that previously have been difficult to treat.[19] These include large medial rectus recessions for large angle esotropia, large superior rectus recessions for dissociated vertical deviations, and extraocular muscle surgery for the treatment of head turn associated with nystagmus.

Although there is a trend toward earlier surgery for infantile forms of strabismus,[20,21] disagreement persists as to the best time for surgery in this group of patients.[22]

Active Force Generation and Forced Duction Tests

The active force generation test directly records the force produced by an extraocular muscle as it attempts to rotate the globe. As a measure of active force, the test provides information on the weakness or strength of an extraocular muscle to aid in surgical decision-making.[23]

Efforts have been made to quantify the forced duction test, which has been useful in identifying mechanical restrictions prior to, during, and after strabismus surgery. Quantification could provide more information for the clinician concerning the nature, extent, and location of the restriction.[24–28]

Drugs

Botulinum toxin has been used to produce selective paralysis of an extraocular muscle. This toxin has been injected into the antagonist of a paralyzed extraocular muscle under electromyographic control to diminish or eliminate temporarily the deviation and prevent contracture of the antagonist muscle.[29] In addition, the toxin has been used to treat strabismus in patients for whom surgery was contraindicated.

Preliminary work has been completed on the use of succinyldicholine during surgery to assist in recreating the preanesthetic strabismic deviation.[30] This study has suggested some of the mechanism of muscle innervation and may eventually prove useful in determining the appropriate amount of strabismus surgery.

Prisms

The availability of Fresnel membrane prisms has opened new avenues in the evaluation and treatment of strabismus.[31,32] By appropriate positioning, vertical and horizontal prism correction may be combined.[33] Several forms of specific sensory influences upon ocular alignment have been recognized, such as the poorly understood changes that occur with the prism adaptation test.[32]

Strabismus Types

The nystagmus blockage syndrome has been described,[34] and a relationship postulated between attempted convergence and dampening of nystagmic eye movements. Also, the relationship of refractive error to strabismus[35] and the effect of strabismus surgery in changing refractive error have both been reported.

Animal Model

A strain of monkey has been found with infantile strabismus that is somewhat comparable to that found in humans (Figure). This may provide a model for studying not only the etiology of strabismus, but also its nonsurgical and surgical treatment.[36] However, the value of this model has yet to be determined.

FIGURE 1. A naturally strabismic infant monkey is being examined as a potential animal model for learning more about the strabismus which occurs in humans. (Photograph courtesy of R. G. Boothe.)

Torsion

There have been some interesting and useful observations comparing the motor and sensory components of cyclofusion.[37–39]

Anterior Segment Circulation

The extraocular muscles carry an extensive portion of the circulation to the anterior segment of the globe. Studies utilizing fluorescein angiography of the iris[40,41] have indicated some of the effects of extraocular muscle surgery upon the vascularity of the iris. This research is especially relevant in cases of patients who have had adjacent rectus muscles or more than two rectus muscles operated upon, and in

those who have had previous muscle surgery in the same eye.

Training

Postresidency training programs have been developed specifically for ophthalmologists interested in specializing in strabismus diagnosis and treatment. This has resulted in an improved level of training for residents and a greater number of full-time faculty in ophthalmology departments interested in research in strabismus and disorders of ocular motility.

RESEARCH NEEDS AND OPPORTUNITIES

Clinical Trials

One of the problems in the management of human strabismus is that various authorities and medical centers approach the problem with their own individual biases, using past experience as a primary guide to the proper therapy. This leads to reports of the efficacy of an individual treatment that are based on experience with limited numbers of patients who have been treated and evaluated in a relatively noncontrolled manner. The result has been the development of various "schools" of strabismus management, each with trainees and disciples believing that their approach is best.

Multicenter studies of strabismus management techniques could be effectively conducted using a protocol agreed upon by the participating centers. The various nonsurgical or surgical techniques employed in the studies could be followed for a given period of time and the results evaluated by a center not involved in the treatment of strabismus. Such studies would be designed with appropriate controls and a minimum of individual bias. Examples of studies that could be performed in a multicenter environment are: (1) early versus late surgery in infantile esotropia, (2) evaluation of the optimum amount of surgical overcorrection in patients with intermittent exotropia, (3) evaluation of the response of the prism adaptation test as a guide to the surgical management of infantile esotropia, (4) evaluation of the several surgical techniques that have been recommended for the treatment of dissociated vertical divergence, and (5) evaluation of the long-term effect of standard strabismus surgery versus adjustable suture surgery. Numerous other management questions could be formulated for study in a multi-institutional clinical trial. To promote the submission and coordination of such investigations, it is recommended that the National Eye Institute organize one or more workshops for participants from interested institutions.

Surgery

Strabismus surgery continues to be a major approach to the treatment of ocular deviations. However, the reoperation rate following the first procedure is about 25 percent, and it becomes even higher for subsequent surgical procedures. Some patients require three, four, or more operations, which entail increased risk, commitment of time to the treatment, and cost.

Anatomy. Continued study of the anatomy of the extraocular muscles and the fascial planes in which they are enveloped would be helpful in developing improved surgical techniques. Previous studies have revealed new and interesting information about the relationship of the oblique muscle to the tenon's connective tissue and to the trochlea.[42] Continued study in this area may produce techniques that promote better healing, reduced scarring, and improved function postoperatively.

Much still needs to be learned about the measurement of the cross-sectional area of an extraocular muscle. What is the importance of this measurement? How is it accurately performed? Where along the muscle is it most important to do the measurement? Should the difference in cross-sectional area affect the amount of muscle surgery planned? Answers to questions such as these can be helpful in planning therapy.

Adjustable Sutures. Other investigations in surgical technique would also be of value. Adjustable suture surgery has been performed on the horizontal rectus muscles and the vertical rectus muscles. Recent studies of the anterior portion of the superior oblique muscle have been promising. Further studies aimed at simplifying the procedure and extending it to younger individuals, and making it possible to adjust ocular alignment even after the first postoperative day could lead to an increased success rate for strabismus surgery and a lowered reoperation rate.

Posterior Fixation Suture. The posterior fixation suture has been introduced as a surgical technique within the past few years and has been reported to be useful for treating dissociated vertical divergence and esotropia with a high AC/A ratio. This procedure also may be useful in strabismus where the deviation is minimal or absent in primary gaze, but where a definite deviation in one direction of gaze (grossly incomitant deviation) occurs. New uses may be found for this surgical technique, and other strabismus problems may respond to treatment with it.

Transposition. When a rectus muscle has become paralytic, ocular rotations into that muscle's field of action are usually severely limited. Standard surgical techniques may successfully eliminate or reduce the deviation in primary gaze but often are not successful in increasing the range of ocular motility. This usually occurs when extensive recession-resection surgery is performed with no beneficial effect on rotation into the field of action of the paralytic muscle. Innovative surgical techniques, including the transposition of the insertion of other functional rectus muscles to the insertion of the paralytic rectus muscle, have improved but not normalized ocular motility. Continued investigation is needed on these and other innovative surgical techniques, such as nerve-muscle transplantation and extension of a recession by transplantation of a segment of extraocular muscle from the same patient or from an eye muscle bank. These approaches might increase the options of the strabismus surgeon and lead to overall improved results.

Modeling. Some work has begun on mathematical modeling of human ocular motility to predict the effect of surgical manipulation of one or several of the extraocular muscles. This approach may help the surgeon make decisions about the muscle proposed for surgery and the amount of surgery to perform. Refining the technique and utilizing the information it yields may lead to more accurate surgical planning and improved surgical results.

Eye Movements

Eye movement studies utilizing electrooculography, infrared reflective techniques, and photography have provided insight into the workings of normal and abnormal oculomotor systems. Information has become available for detecting early eye movement abnormalities in several neurologic diseases and for identifying and evaluating paresis of an extraocular muscle. Studies of this kind should be continued and expanded. The simplification of eye movement recording techniques, while maintaining accuracy, would improve their usefulness to the clinician in evaluating patients with such abnormalities. Easily operated and relatively inexpensive devices could provide readily accessible information to the strabismologist that would allow him or her to understand eye movement abnormalities more thoroughly and plan appropriate therapy.

Forced Traction and Active Force Generation

The forced duction test is extremely useful for evaluating the passive ability to rotate the eye in a horizontal, vertical, or oblique direction. It is used to evaluate the mechanical limitations to full rotation of the globe that may be caused by systemic disease, such as thyroid disease, ocular trauma such as orbital floor fracture, congenital abnormalities such as Brown's syndrome, or previous extraocular muscle or retinal detachment surgery. Knowledge of these restrictions is extremely important in determining the proper amount of surgery, the muscles to be operated upon, and the treatment of the conjunctiva and the underlying tenon's capsule. The ophthalmologist generally performs this technique in the operating room when examining infants and young children, and under topical anesthesia when examining cooperative teen-age and adult patients. The technique requires the use of a fixation forceps to fixate the globe at a location adjacent to the limbus and then following the arc of rotation to move the globe into the desired position. Because the test is performed in a qualitative, rather than quantitative manner, and interpretation of the results is subject to the examiner's knowledge, skill, judgment, and other factors, the test is useful primarily to the experienced clinician.

Modification of the technique and instrumentation to allow quantitative performance of the forced traction test, both in the outpatient and operating room settings, could be a useful advance in strabismus evaluation. Again, an instrument that is relatively easy to use and whose results are easy to interpret would be desirable. The development and evaluation of a practical device of this type would help make the diagnosis and management of some forms of strabismus less empirical and more scientific. Similarly, instrument and technique development for the active force generation test, which can now be done only in cooperative teen-age and adult patients while alert and awake, would also be a great step forward. This technique allows the measurement of voluntary, actively generated force, not passive rotations, and provides information on the innervational rather than mechanical aspects of ocular rotations.

Measurement of Alignment

Present measurements of the ocular deviation and rotations in adults are quite accurate. These patients can cooperate with the examiner and provide subjective responses that can be exquisitely sensitive and exact. However, in infants and young children, subjective information is more difficult, if not impossible, to obtain. Current methods for examining muscle balance depend on observations of the light reflex from the young patient's eye or from cover test measurements which may be difficult to do and which may give inexact results. In general, the development of examination techniques and instrumentation for the improved measurement of ocular deviations and ocular rotations could be of

great assistance to the ophthalmologist in evaluating strabismic patients.

Stability of Therapy

Nonsurgical and surgical treatment strategies in strabismus have frequently emphasized the immediate and short-term effect of the treatment. However, changes in ocular alignment sometimes occur over a long period of time, and clinical studies of the long-term stability of treatment results and of possible ways to maintain that stability would be most useful. In addition, studies of the diagnosis and further treatment of patients who have had multiple previous surgeries and require reoperation, could reduce the number of operations performed on many such patients.

Not infrequently, there may be sensory obstacles to the attainment of normal ocular alignment and binocular vision, including amblyopia, anisometropia, and suppression. Continued investigations of the role of these obstacles might help to explain why some types of therapy are more successful than others, and why certain patients receiving a given therapy seem to do better than others. Of additional interest are the mechanisms that produce a change in ocular alignment in response to prism therapy, either to the exact amount of prism correction or to prisms that overcorrect the angle of the deviation. Better understanding of the responsible mechanism could lead to more precise therapeutic decision-making and result in more accurate and stable alignment. This will require clinical studies utilizing both psychophysical and electrophysiological methods.

Torsion

It is generally recognized that patients with symptoms due to ocular torsion have more than 5 or 6 degrees of cyclotorsion (usually found in bilateral superior oblique palsy). Smaller degrees of cyclotorsion are often not recognized. In normal subjects, torsional diplopia is usually not produced by testing with instruments such as the troposcope until at least 5 degrees of cyclotorsion are induced. Further investigation of the nature of sensory adaptation to cyclotorsion could provide more information concerning the adaptive nature of the patient's compensation and could help in treating torsional deviation, or at least minimizing the deviation to the point where it is not noticed by the subject.

Identification of Risk Factors

Strabismus has been described as having multifactorial inheritance. Offspring from families with a strong history of strabismus are more likely than others to develop strabismus or pass it to their immediate offspring. Methods to identify and investigate the infant at risk for strabismus, even before strabismus has developed, remains a great need to the ophthalmic clinician. More information about the epidemiology of strabismus and its genetic aspects could be of tremendous assistance in identifying infants at the greatest risk, thus providing a basis for low-cost screening techniques that would be applicable to a limited population. Preliminary data in children have indicated that ocular vestibular testing and/or brainstem-evoked potential recording may be able to pinpoint abnormal brainstem function related to strabismus. Continued studies of these or other objective testing methods could radically improve methods of identifying strabismic infants, making it possible to prevent some of the complications of untreated strabismus. In addition, more sensitive and cost-effective screening methods should be developed for detecting strabismus in infants.

Animal Model

Now that an animal model of strabismus has been found in a colony of monkeys, there are several new opportunities for investigation. Electrophysiological testing of cortical function as well as gaze center function may be performed in animals with strabismus; hitherto, this has not been possible. In addition, various experimental methods of therapy could be tested in this group of animals, including innovative techniques such as nerve muscle transplantation and various types of transposition surgery. This animal model also may supply further knowledge of the cause of human strabismus.

Nystagmus

Patients with nystagmus have a constant, oscillating movement of the eyes, which invariably leads to reduced vision. Nystagmus may be congenital in origin or may be acquired secondary to neurologic disease. Congenital nystagmus results in not only poor vision because of the constant ocular movement, but it probably also causes amblyopia after the age of 6 or 7. Beyond this age, such patients would not be likely to achieve normal acuity, even if their ocular oscillations could be stopped. Studies of the cause of nystagmus and its possible medical and surgical therapy would be of great value in this group of patients, who otherwise appear to have permanently reduced visual function. Although some depressant drugs have been able to quiet nystagmus, the dosage generally has been too great to allow the patient to function normally. Further investigation may be useful in discovering a drug

that can have a dampening effect upon eye movement without generally affecting cerebral function.

Strabismus Patterns

A number of specific forms and patterns of strabismus are poorly understood. For example, sensory strabismus that develops in older people is invariably of the exotropic variety, whereas most strabismus in infants, especially that of a sensory nature, tends to be of the esotropic type. Why this occurs is still unclear. In dissociated vertical divergence, the occluded eye or the eye not attentive to the target drifts upwards. This type of eye movement behavior does not follow Herring's law, which would predict equal and symmetrical or parallel movements in the two eyes, and is difficult to understand. Furthermore, experience with dissociated vertical divergence indicates that rather extensive surgery is necessary to gain even modest effects. Recent descriptions have helped in the diagnosis of dissociated vertical divergence and in distinguishing it from its look-alike, inferior oblique overaction. Although dissociated vertical divergence is strongly associated with congenital esotropia, the reason for this association and for its occurrence is not well understood. Investigations into the normal development and function of the oculomotor system may help to clarify abnormal development and function; and conversely, a fuller understanding of these clinical entities may lead to a better basic understanding of the specific function of both normal and abnormal extraocular muscles and the surrounding connective tissue attachments in the orbit.

Drugs

Botulinum toxin injection into an extraocular muscle produces a temporary muscle weakness, the extent and time of which is dose related. This technique has been applied usefully in patients for whom surgery may be contraindicated and to weaken the antagonist of a paralytic muscle to prevent contracture. In some instances, the need for surgery has been obviated; in others, surgery has been performed subsequently under more ideal circumstances that avoid secondary mechanical changes. Continued study of botulinum toxin and other drugs is needed to explore further the usefulness of this approach and the situations in which drug therapy can be best applied.

Anterior Segment Vascularization

Research is needed for better understanding of the vascular patterns of the anterior segment of the eye. Not only is it necessary to know the changes that take place with age, but also the alternate routes of circulation that develop following various combinations of extraocular muscle surgery and the patterns that occur with reoperations. Previous studies have utilized fluorescein angiography of the iris. This approach is successful with light-colored irides but does not work well with a heavily pigmented iris. Alternate techniques that could be applied to all patients would be useful.

Training

Another area that requires support is the training of clinician-investigators interested in strabismus and ocular motility. Clinical training centers that exist in several cities (for example, Washington, Indianapolis, Iowa City, Houston, San Francisco, Los Angeles, and Philadelphia) emphasize practical, clinical training in strabismus. However, few of these centers emphasize the related basic science training that could improve the quality of investigations of ocular motility. Opportunities could be provided for clinician-investigators to broaden their experience, especially with training grant support from the National Eye Institute, and to produce trainees with skills and capabilities in research and clinical disciplines. This type of training is important for upgrading research opportunities in this field.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Strabismus," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base consists of an area of ongoing research in which the current level of activity is considered adequate. Nonetheless, additional research grants in this area may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Base

- Study the sensory/perceptual consequences of strabismus.

Program Development Priorities

- Conduct clinical investigations of surgical treatments for strabismus. Possible problems for study include (1) asymmetric versus symmetric surgery, (2) usefulness of force measurements in strabismus surgery, (3) development of new materials and techniques to minimize postoperative restrictions in adhesive strabismus.
- Study pharmacological and other approaches to the treatment of strabismus, including the short- and long-term effects of drugs on extraocular muscles.
- Investigate the importance of sensory stimulation for changing the angle of strabismus.
- Study the importance of the chronology of treatment methods and the effect on outcome. This will require knowledge of the critical period for developing fusion and altering the angle of strabismus.
- Continue genetic and epidemiologic studies of risk factors for strabismus.
- Develop better quantitative eye movement recording techniques to improve diagnosis of various forms of strabismus.
- Develop appropriate animal models as aids to understanding the sensory and motor deficits of strabismus.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

OCULAR MOTILITY AND STRABISMUS

Disorders

STRABISMUS

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Base			
A. Study the sensory/perceptual consequences of strabismus.	3	0	3
Program Development Priorities			
A. Conduct clinical investigations of surgical treatments for strabismus.	2	1	3
B. Study pharmacological and other treatments of strabismus.	2*	3	5
C. Investigate importance of sensory stimulation for changing angle of strabismus.	0	2	2
D. Study importance of chronology of treatment for outcome.	0	2	2
E. Continue genetic/epidemiologic studies of risk factors for strabismus.	1	1	2
F. Develop better quantitative eye movement recording techniques to diagnose strabismus.	0	1	1
G. Develop animal models of strabismus.	1	5	6
Subtotal Grants	**9**	**15**	**24**
(% of Program)	**(4)**	**(18)**	**(7)**
Total Estimated Cost	**$618,000**	**$1,734,000**	**$2,352,000**

*Includes one single-center clinical trial: Chemical Alteration of Extraocular Muscle Function.

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10

MOTOR NEURO-OPHTHALMIC DISORDERS

INTRODUCTION

THIS CHAPTER IS concerned with research on all acquired or congenital eye-movement disturbances exclusive of strabismus. Included are: all forms of nystagmus and other types of ocular oscillations, such as overshoot dysmetria, ocular flutter, flutter dysmetria, opsoclonus, square wave jerks, macro square wave jerks, macro saccadic oscillations, superior oblique myokymia, and spasmus nutans; gaze disturbances; oculomotor apraxia; neuropathies of the third, fourth, and sixth nerves; ocular myopathies; and neuromuscular transmission disturbances affecting the ocular muscles such as myasthenia gravis and the Eaton-Lambert syndrome.

The basic purpose of most conjugate eye movement systems is to prevent excessive image motion on the retina, which would otherwise impair vision. Disorders of these systems may be broadly classified as those that fail to act correctly in the appropriate circumstances and those in which unwanted eye movements, such as oscillations, occur spontaneously.

Disorders of the former kind are caused by many types of lesions of the cerebellum, pons, mesencephalon, and the vestibular organs that interfere, for example, with the ability to hold eccentric gaze, generate pursuit movements, or produce adequate vestibular compensatory movements. Examples of spontaneous oscillations are downbeat nystagmus, periodic alternating nystagmus, ocular flutter, and congenital nystagmus. All of these latter disorders cause the images of objects in the visual environment to move on the retina and interfere with visual function (Figure 1). Depending on the velocity of retinal image motion, the resulting visual impairment may be slight or it may be so severe that the patient cannot read, drive a car, or hold a job.

Disorders that involve involuntary eye movements or the vestibular apparatus can also produce illusory movement of the environment and dizziness, which can be incapacitating. Obviously, the more that is known about the structure, organization, and neurochemistry of these systems, the easier it will be to prevent, diagnose, and repair their disorders.

Certain other disturbances, including gaze palsies, internuclear ophthalmoplegias, and the cranial neuropathies, also affect vision but are important mainly because they provide clues to the diagnosis and treatment of serious underlying neurological disturbances such as multiple sclerosis, stroke, and

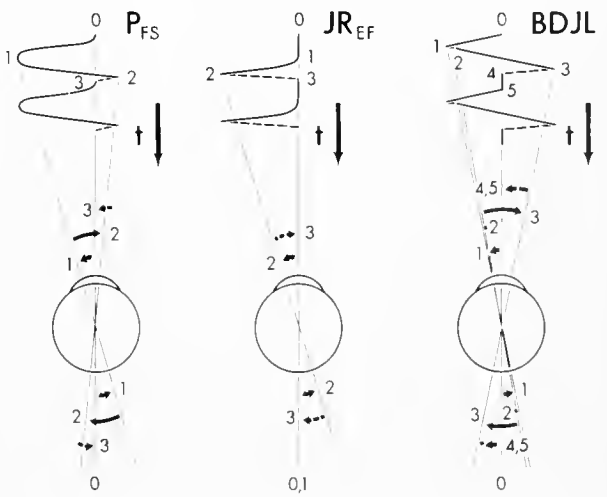

FIGURE 1. Effects of three forms of congenital nystagmus on foveation. In some forms, compensatory mechanisms result in extended foveation with resultant optimization of visual acuity. (P_{FS} is pendulum nystagmus with foveating saccades, JR_{EF} is jerk right nystagmus with extended foveation, and BDJL is bidirectional jerk left nystagmus. The time scale is represented by t). (Diagram reprinted from Daroff et al: Nystagmus and related ocular oscillations, in Glaser JS (ed): *Neuro-Ophthalmology*, Hagerstown, Harper & Row, 1978.)

brain tumors. Consequently, astute observation of abnormal eye movements can often help the physician locate a lesion. The functional importance of many brainstem and cerebellar structures has been discovered through basic research, especially in the last ten years. In some cases, this research has provided mechanistic explanations for disordered eye movements, revealed more subtle movement disorders, and demonstrated more clearly the diagnostic significance of abnormal eye movements. Much more research in this area should be done.

Ocular myasthenia is frequently a serious visual handicap and often poses a significant cosmetic and therefore psychological problem as well. But studies of this disorder are most important because they assist the diagnosis and treatment of the generalized, and potentially crippling, form of myasthenia gravis.

Oculomotor control is considered by many to be a simplified model of motor control in general, and what is learned from research on the former may have relevance for the latter. For example, given the rate of current progress, it is possible that the function of the cerebellum in the control of eye movements will soon be understood. Such knowledge will likely lead to an understanding of its role in the control of body and limb movements. Although such research has as its immediate goal the attainment of knowledge that could be beneficial to patients with eye movement disorders, it has a larger significance because of the potential of its contributions to the disciplines of neurophysiology and neurology, and eventually to society in as yet unknown ways.

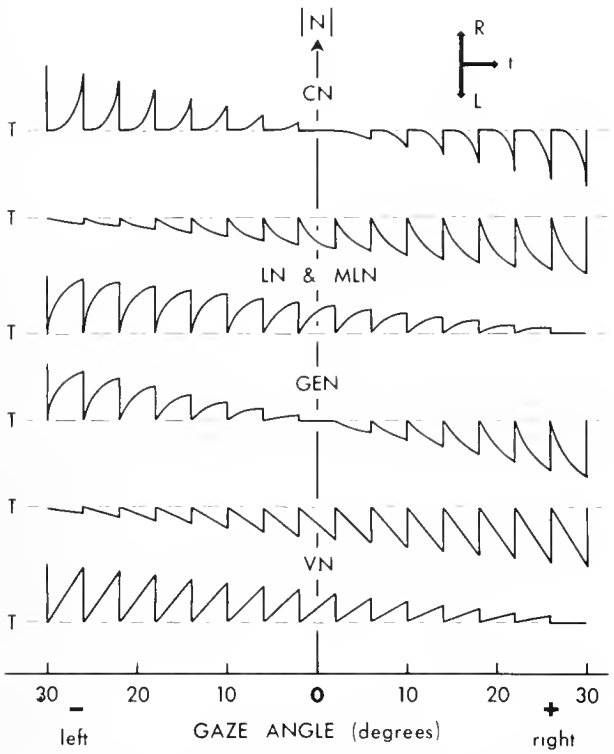

FIGURE 2. Variation with gaze angle of magnitude (N) of congenital (CN), latent and manifest (LN and MLN), gaze evoked (GEN), and vestibular (VN) nystagmus. In CN, the slow phases are increasing velocity exponentially, whereas in LN, MLN, and GEN, the velocity is exponentially decreasing. In VN the slow phases are linear. (R:right; L:left; t:time). (From Dell'Osso et al. *Arch Ophthalmol* 97:1877-1885, 1979.)

Through careful eye movement recording and wave-form analysis, the different forms of nystagmus are beginning to be recognized (Figure 2). Congenital nystagmus and manifest latent nystagmus (a congenital form of nystagmus) can be distinguished from nystagmus acquired secondary to neurological disease, but congenital nystagmus cannot be distinguished from nystagmus developing in early life secondary to progressive visual loss. On the basis of wave-form analysis and correlations with both neurophysiological information from animal experimentation and servo-system modeling by biomedical engineers, the mechanisms of all forms of nystagmus and other oscillations are beginning to be understood. With a reasonable degree of certainty, myasthenia gravis can be diagnosed by eye movement recordings. Diagnosis of other conditions, including those with significant genetic and therapeutic implications such Huntington's disease and Wilson's disease, may be assisted by careful eye movement recording. Similarly, the diagnosis of multiple sclerosis is facilitated by such recordings.

Visual acuity in some patients with congenital nystagmus can be improved with prism spectacles and/or surgery. However, except for acquired periodic alternating nystagmus and superior oblique myokymia, ocular oscillations cannot be treated effectively with drugs.

Research in this area of neuro-ophthalmology is clearly related to research on other aspects of the sensory and motor disorders of vision, specifically to the human disorders of visual processing and amblyopia, structure and function of ocular motility, and strabismus. To the extent that neuro-ophthalmic ocular motility disorders are secondary to specific diseases, research into such diseases as multiple sclerosis, myasthenia gravis, and central nervous system disorders in general is clearly related. Furthermore, all research into the vestibular system and its disturbances is strongly related to neuro-ophthalmic motility disorders.

SUBPROGRAM OBJECTIVES

- To improve the ability to diagnose motor neuro-ophthalmic disorders.
- To determine the most cost-effective methods of diagnosing neuro-ophthalmic disorders of ocular motility.
- To improve methods for treating those conditions.

OVERVIEW OF CURRENT RESEARCH SUPPORT

Only four extramural projects, at a total cost of $265,000, and a few intramural projects were supported by the National Eye Institute in this subprogram in FY 1981. This situation probably reflects the fact that the National Institute of Neurological and Communicative Disorders and Stroke supports most clinical studies involving the vestibular system and the Veterans Administration supports systematic research of this type in at least one major laboratory.

However, the scant number of extramural NEI projects in this area also reflects the small number of proposals received. This, in turn, indicates that an inadequate number of clinical centers around the country are capable of performing quantitative oculography.

RECENT ACCOMPLISHMENTS

Major clinical advances have been made through the utilization of quantitative eye movement recording (oculography) in patients with abnormal eye movements. This has permitted precise characterization and analysis of the wave forms, in contrast to previous reliance on clinical descriptions of eye movements, which often precluded meaningful analysis and classification. Better understanding of abnormal eye movements has been attained as a result of information obtained from the many studies of normal eye movements as well as the physiological, anatomical, and controlled system advances that are discussed in Chapter 6, "Conjugate Eye Movements." Conversely, clinical studies help basic scientists clarify control system and physiological conceptualizations and provide them with ideas for future basic research. Thus, a considerable interdependence between basic and clinical research exists in the field of neuro-ophthalmological motility disturbances.

Congenital nystagmus has been the most precisely studied of the oscillations. The studies have led to therapy with prism spectacles [1] and a more precise definition of the role of surgical correction [2] in this disorder. Without quantitative oculography, this potentially correctable form of nystagmus cannot be distinguished from manifest latent nystagmus, [3] which is not amenable to surgery. In patients in whom surgery for congenital nystagmus failed, as reported in the literature, oculography was not used, and this may explain the failures. Recently, attempts have been made to diminish congenital nystagmus with auditory feedback control. [4]

Other specific oscillations that have been characterized with oculography and correlated with neurophysiological experimentation and systems modeling are overshoot dysmetria, [5] flutter, [6] macrosaccadic oscillations, [7] macro square wave jerks, [8] and voluntary nystagmus. [9]

The simultaneous recording of head and eye movements is a recent accomplishment that is beginning to bear fruit. [10] It is a more physiological manner of studying eye movement disturbances because heads are not fixed but move freely. Single case reports of such head and eye recordings in patients with congenital nystagmus and spasmus nutans have provided information that was totally unexpected from clinical observation alone. In the case of congenital nystagmus, [11] the associated head movement was neither compensatory nor anticompensatory; it was a superimposed oscillation which, coupled with the vestibulo-ocular reflex, did not affect foveation or acuity. However, head oscillation in the patient with spasmus nutans [12] seemed to have completely stopped the eye-in-head oscillation and was therefore extraordinarily compensatory. Studies of eye and head movements in congenital oculomotor apraxia also yielded unexpected information. [13] Previous reports, based upon clinical observation and photography, indicated that the patients turned their heads with a thrusting motion, dragging their eyes passively and utilizing the vestibulo-ocular reflex; the primary defect was thought to represent an absence of saccades. A recent study [13] demonstrated that the patients had difficulty initiating saccades with fixed heads but could do so when the head was thrust in the direction of the new intended line of sight.

Many eye movement disturbances, whether static or dynamic, represent a failure of central nervous system plasticity or an admixture of the pathological oscillation upon plastic alterations. [14–16] The longitudinal studies that have been performed have provided important inferences regarding the functional

capability of the central nervous system to alter and correct derangements (see Chapter 6).

The introduction of full field optokinetic stimulation is an important advance in studying this presumably separate eye movement system. Only preliminary studies of this system, comparisons with foveal optokinetic nystagmus, and correlations with smooth pursuit function have been undertaken [17] (see Chapter 6).

The introduction of a new clinical test, vestibulo-ocular reflex (VOR) suppression, has added an important tool to clinical diagnosis. [18,19] This test is performed by having a subject rotate while viewing a similarly rotating target. Normal subjects can suppress the VOR but those with impaired pursuit cannot. The exact correlation of this phenomenon with the integrity of various aspects of oculomotor function is presently unknown (see Chapter 6).

Considerable attention has been given to the concept of correlating object and self motion preception with vestibular, visual, somatosensory, and oculomotor control. [20,21] This has the potential of significant clinical relevance as further studies define the multisystem interrelationships.

The drug baclofen, a synthetic analog of GABA, stops acquired periodic alternating nystagmus [22] (see Chapter 6). As other drugs that affect synaptic transmission are developed and knowledge of the neural transmitters involved in oculomotor control increases, the development of drug therapy for other ocular oscillations may be possible. The only other example of an oscillation known to respond significantly to a drug is superior oblique myokymia, which usually ceases after administration of carbamazepine. [23]

As mentioned earlier, a number of specific disease states such as progressive supranuclear palsy, [24] cerebellar degeneration, [19,25] multiple sclerosis, [26,27] and myasthenia gravis [28,29] characteristically affect eye movements. Studies of these eye movement disorders have provided insights into mechanisms and, more importantly, have facilitated diagnosis of the underlying disease.

Mitochondrial abnormalities have been observed in the skeletal and extraocular muscles of patients with progressive external ophthalmoplegia and subtypes of this disease have been tentatively identified. [30] These findings suggest the possibility of a better classification and etiological determination of this poorly understood group of disorders.

RESEARCH NEEDS AND OPPORTUNITIES

This section is divided into four general areas: technology, disease entities, therapy, and pathophysiological mechanisms.

Technology

At present, eye movement disturbances in early infancy defy quantification. Methodology should be developed for such studies (see Chapter 8, "Strabismus").

Some reports have encouraged the use of computerized eye movement screening in patients with suspected central nervous system disease. Computer analysis has been used for saccadic, smooth pursuit, optokinetic, and vestibulo-ocular testing. This provides quick, although expensive, results. Whether or not such computer analysis provides information beyond that obtainable by a trained neurologist or neuro-ophthalmologist during a simple clinical examination should be determined. If the physician does as well, it might be more cost-efficient to increase the clinical training of physicians than encourage proliferation of extremely expensive instrumentation.

Despite the fact that almost all the recent advances in neuro-ophthalmic eye movement disorders are dependent, at least in part, on quantitative eye movement recording, only a few laboratories in the United States are capable of such recordings. Many large cities do not have any laboratory capable of accurate high band width DC oculography, which is necessary for quantitative studies. The scarcity of such facilities relates primarily to a lack of trained personnel. More biomedical engineers should be trained in clinical eye movement analysis, and more clinicians should obtain biomedical engineering training. The difficulty of obtaining funding for such postgraduate or postresidency training should be corrected, possibly with the reestablishment of training grants for those few laboratories capable of providing training in instrumentation, methodology, and clinical analysis.

The diagnostic capabilities of different eye movement recording techniques should be determined. The usefulness of AC oculography, low band width versus high band width DC oculography, infrared oculography, and contact lens magnetic search coil techniques, should be determined. This can be done only when these techniques are used in the same laboratory to study patients with varying disturbances. Such information will permit development of new laboratories with instrumentation suited best for their particular needs in clinical diagnosis.

Encouragement should be given to the development of automatic technology in eye movement recording, so that technicians can perform the tests. Present technology demands more highly trained personnel.

Disease States

In a number of diseases, diagnosis and treatment depend heavily upon eye movement analysis. These include multiple sclerosis, myasthenia gravis, stroke, Meniere's disease and other forms of vertigo, congenital nystagmus, certain forms of brain tumors, Parkinsonism, and Huntington's disease. Thus, eye movement research has a significant impact on a large patient population.

Continued quantitative recording of eye movement disturbances, including the various forms of nystagmus, particularly those of infancy and childhood, is needed to clarify mechanisms, facilitate diagnosis, and evaluate treatment. As yet, there is no way of determining whether nystagmus in infancy is secondary to visual loss or whether it is a congenital motor abnormality co-existing with the primary visual disturbance. In particular, the eye movements of nystagmus patients need to be studied with reference to wave form in both open loop (darkness) and closed loop (illuminated) conditions. The latter, which simulates real life conditions, may represent the effect of an optokinetic counterstimulus acting on the slow phase shape. Only with open loop recordings can the essential instability responsible for the oscillation be isolated. Nonnystagmus oscillations such as dysmetria and myoclonus also require further study. In the latter type of disturbance, no good recording exists in the literature to substantiate the widely held presumption that it is a pendular oscillation.

Additional free head and eye movement studies must be encouraged in a variety of static and dynamic eye movement disturbances. As mentioned, there have only been single case reports in congenital nystagmus [11] and spasmus nutans. [12] The relationship between eye and head movements in both these conditions must be studied in larger patient groups. Further research on congenital oculomotor apraxia is required to determine if there are different subtypes of this malady; that is, whether there are patients who have a global saccadic paralysis and who require head movement to drag the eyes in addition to those studied who can initiate saccades provided a head thrust precedes the refixation. [13] In both congenital oculomotor apraxia and spasmus nutans, there is a distinct change over time. In the latter, the oscillation disappears, whereas in the former, the head-eye relationship seems to change. The nature of these changes over time have never been studied quantitatively; such studies should be encouraged.

Further studies of the perceptual concomitance of oculomotor disorders involving self motion perception, object motion perception, and localization of objects in space are required. These should be done in patients with known vestibular, peripheral, and central nervous system lesions. Tests of otolithic function and dysfunction should be developed. There is a large number of patients with unexplained vestibular symptomatology that could relate to otolithic dysfunction, but at present otolith function cannot be reliably tested clinically.

Quantitative studies of the eye movements in peripheral, neuromuscular, and muscle diseases must be continued to refine diagnostic capabilities.

Therapy

In congenital nystagmus, continued investigations of the precise use of prisms, extraocular muscle surgery, and auditory biofeedback must be encouraged.

Some of the previously mentioned diseases in which eye movement analysis is important for diagnosis, such as myasthenia gravis and Parkinsonism, can be treated with drugs. Studies should be encouraged that use oculography to quantify the success of treatment. Moreover, oculography can be used to assist in the development of therapy for many conditions which, at present, are not adequately treated; these include multiple sclerosis, stroke, Huntington's disease, and most forms of vertigo.

Drug treatment of nystagmus and other ocular oscillations should be encouraged when new agents are introduced.

Pathophysiological Mechanisms

All abnormal ocular oscillations must be better correlated with the site of anatomical dysfunction, oculomotor modeling, and the effects of central nervous system plasticity (see Chapter 6). With respect to plasticity, tests of adaptive capability must be developed as a means of probing the functional integrity of various parts of the nervous system. This can be done, for instance, by using reversing prisms and determining adaptability in patients with various lesions of the central nervous system. Similarly, adaptation to the pulse and step components of saccadic dysmetria can be tested experimentally using optical methods. Quantification of the habituation of vestibular responses can also become a diagnostic test if further refined.

Vestibulo-ocular reflex suppression should be studied and correlated with other oculomotor functions to define better the utility of this test. Similarly, foveal pursuit, foveal optokinetic nystagmus, and full field optokinetic nystagmus require study in patients with a variety of neurological

conditions and lesions. Only in this way can normal or pathological interrelationships among foveal and extrafoveal pursuit and optokinetic nystagmus be understood.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Motor Neuro-Ophthalmic Disorders," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have been grouped under two headings: Program Base and Program Development Priorities.

The Program Base consists of an area of ongoing research in which the current level of activity is considered adequate. Nonetheless, additional research grants in this area may be funded if they are innovative and of very high quality as determined by the NIH peer review system.

Program Development Priorities include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Base

- Study the cellular aspects and system modeling of neuro-ophthalmic diseases.

Program Development Priorities

- Encourage continued quantitative study of eye movements in a variety of central and peripheral neurological diseases. These studies should be designed primarily to facilitate diagnosis, aid in the design of possible treatments, and provide explanations of the disorders.
- Determine the cost-effectiveness of computer analysis of oculomotor functions compared to clinical analysis by trained neuro-ophthalmologists.
- Develop new technology for automated eye movement recording systems.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

OCULAR MOTILITY AND STRABISMIS

Disorders

MOTOR NEURO-OPHTHALMIC DISORDERS

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Base			
A. Study the cellular aspects and system modeling of neuro-ophthalmic diseases.	2	0	2
Program Development Priorities			
A. Study of eye movements in neurological diseases.	2	2	4
B. Compare computer analysis of oculo motor functions with clinical analysis by a trained neuro-ophthalmologist.	0	1	1
C. Develop new technology for automated eye movement recording systems.	0	2	2
Subtotal Grants	**4**	**5**	**9**
(% of Program)	**(1)**	**(6)**	**(2)**
Total Estimated Cost	**$265,000**	**$617,000**	**$882,000**

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OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA

11

OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA

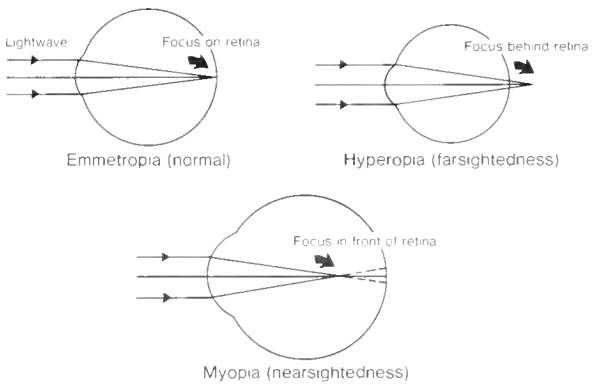

FIGURE 1. Refraction in the normal eye compared with hyperopia and myopia.

INTRODUCTION

REFRACTIVE ERROR OF the eye may be defined as the eye's failure to form a focused image on the retina because of an improper combination of the power and spacing of its optical components. Types of refractive error include myopia, hyperopia, aphakia, astigmatism, and presbyopia.

Myopia, or nearsightedness, occurs either if the optical power of the eye is too strong (refractive myopia), or if the eye itself is too long (axial myopia). In both types of myopia, the image comes to focus in front of the retina (Figure 1). Most myopia is of the second type which may progress rapidly, especially in the teen-age years, due to eyeball lengthening, and may require increasingly powerful corrective lenses. Occasionally, very extreme and rapidly developing myopia occurs that may cause retinal damage from excessive stretching of the retina and supporting tissues. Such rapidly progressing myopia is called "progressive," "malignant," or "pathological" myopia.

Hyperopia, or farsightedness, occurs if the optical power of the eye is too weak, or if the eye itself is too short. Most hyperopia is a combination of these two types, refractive hyperopia and axial hyperopia. In hyperopia, the image is formed "behind" the retina (Figure 1), producing a blurred image on the retina itself. A special type of high hyperopia is the condition termed "aphakia" resulting from the removal of a cataractous lens. As a rule, an aphakic

eye has high refractive hyperopia, three or four times greater than ordinary hyperopia.

Astigmatism results from nonuniform curvature of the eye's optical surfaces. Focused images are not formed in any location, on or off the retina. If there are two predominant directions of curvature at right angles to one another, the condition is termed "regular" astigmatism, and this can usually be corrected optically. If, however, the curvature varies in an irregular fashion, as with corneal scars, the astigmatism is termed "irregular" and may be difficult to correct.

Presbyopia is the loss of ability to change the focus of the eye from one viewing distance to another. Presbyopia occurs with age, usually appearing in the early to mid 40s. Bifocal glasses are commonly used to provide proper focusing for reading.

Research on the optics and refractive errors of the eye encompasses studies of the development, prevention, measurement, and correction of refractive errors. As the mechanisms underlying the development and change of refractive errors are defined, preventive measures can be formulated and tested.

The optical components of the eye develop and grow at different rates, but the combined optical effect of these components normally remains remarkably correct throughout development. Experimental study of both normal and abnormal growth processes is extremely important in understanding the development of refractive errors, and ultimately in preventing them. Methods of study include population and other epidemiological research, development of animal models, biomechanical analyses of the forces exerted on the various components of the eye, and biochemical investigation of the tissues involved in determining the shape and optical characteristics of the eye. In addition, clinical trials play an important role in evaluating proposed means of controlling the development of refractive errors.

Approximately 60 percent of the total U.S. population wear corrective lenses at least part-time, and approximately 32 percent of the population wear corrective lenses during all waking hours. [1] At least 90 percent of the population over age 45 wear corrective lenses at least part-time, primarily because of the onset and progression of presbyopia after age 40. An additional percentage of the population, perhaps 10 percent, could benefit from corrective lenses if they had the means and opportunity to obtain them. [1]

In a study of more than 500 grade-school children, [2] approximately 20 percent were found to have an uncorrected, or inadequately corrected, refractive error. In spite of concerted school campaigns by numerous organizations, refractive error in schoolchildren remains a significant cause of decreased learning, with a resulting burden to society.

An inordinate amount of time is spent by ophthalmologists and optometrists in diagnosing and correcting refractive errors. In 1976, refractive errors alone were the cause of 29 percent of visits to ophthalmologists [3] and a much higher percentage of visits to optometrists. In 1975 alone, approximately 48 million refractive examinations were performed in the United States by ophthalmologists and optometrists, [1] for an average of 1,550 examinations per year per practitioner, and an average of six or seven examinations per working day. A refractive examination requires 10 to 30 minutes. At a conservative cost of $20 per refractive examination, the consumer cost of refractive examinations in the United States is roughly $1 billion per year.

It is estimated that glasses are replaced on an average of every three years at an average retail cost for a pair of glasses of $40. Thus, the cost of glasses alone in the United States is roughly $1.5 billion per year.

Obviously, the prevalence of refractive errors is far higher than that of any other class of ophthalmic disorders. Refractive errors are so common that they are sometimes dismissed as simply variations of normal, not disorders or diseases at all. On the other hand, refractive errors certainly create significant problems for a large number of people; the loss of productivity and function due to refractive error may be said to rival that due to headache or the common cold. This report will treat the presence of a significant refractive error as an ophthalmic disorder, one which deserves our best efforts for detection, measurement, correction, and eventual prevention.

SUBPROGRAM OBJECTIVES

- To identify the mechanisms responsible for the control of eye growth and the development of refractive errors, including myopia, hyperopia, astigmatism, and presbyopia.
- To prevent or control refractive changes with maturation and aging.
- To aid the development and testing of instrumentation for effective screening and for rapid and accurate measurement of refractive error of the eyes, especially in young children.

OVERVIEW OF CURRENT RESEARCH SUPPORT

Although research on some facets of optics and refractive errors has been supported by the NEI Corneal Diseases program and the Retinal and Choroidal Diseases program, the National Eye Institute has supported little research aimed toward the objectives listed above. Three grants were funded in this area in FY 1981 at a total cost of $261,000, only one percent of the grants awarded in the Strabismus, Amblyopia, and Visual Processing program. These three grants involved the investigation of animal models for the development of axial myopia. One project which was active in FY 1981 but received no money that year deals with the characterization of astigmatism and the accommodative behavior of infants. Although the NEI-supported grants do address the first two Subprogram Objectives, no other current source of funding exists for such work, and these objectives cannot be met within at least the next 20 years with the present level of activity.

Retinal disease resulting from progressive myopia is an additional concern and is dealt with in *Volume Two, Part One, Report of the Retinal and Choroidal Diseases Panel*, Chapter 6, "Retinal Detachment and Vitreous Disorders."

Research on the measurement of refractive errors is now mostly conducted by physicists and engineers, often outside the medical environment. Significant advances in the application of photoelectronics and microcomputers to the field of clinical refraction have led to the development of instrumentation which each year is becoming more useful to the refractionist.

Research in the correction of refractive errors has been closely tied to commercial interests, and much of the development in this area has been supported directly by industry. The development of some of the instrumentation mentioned in the third objective will likely be accomplished within five to ten years as a result of commercial competition alone.

On the medical side, the various forms of refractive correction have become the province of specialists dealing with different parts of the eye. Research on contact lenses and refractive keratoplasty has been adopted by the corneal specialists, while intraocular lenses have largely been investigated by cataract surgeons. (Research in these areas is described further in *Volume Two, Part Two, Report of the Corneal Diseases Panel*, Chapter 3, "Refractive Problems and Contact Lenses" and in *Part Three, Report of the Cataract Panel*, Chapter 7, "Treatment of Cataract and Correction of Aphakia").

There is no known support from any other U.S. government agency, other than by the National Eye Institute, toward the above objectives.

RECENT ACCOMPLISHMENTS

Population studies have produced basic knowledge of the distribution of refractive errors and the changes in refractive errors with age. The average eye is hyperopic at birth and begins changing in the myopic direction in mid-childhood, at about age 6 or 7. Mild to moderate amounts of hyperopia can easily be compensated for in childhood by accommodation, without symptoms or the need for corrective lenses. The major problem is the development of myopia, which does require corrective lenses. Whether an eye becomes myopic depends on how hyperopic it was to begin with and how much change occurs in the myopic direction.

Recently developed animal models are contributing significantly to knowledge of myopia development. In 1977, Wiesel and Raviola [4] reported that lid closure in young monkeys led to the development of axial myopia, probably through elongation of the eye, when the animal is raised under normal lighting conditions (Figure 2). Subsequent papers by the same authors [5,6] have confirmed that this is a useful animal model for the development of axial myopia. Similar observations have been made by Sherman et al [7] of lid closure in the tree shrew (Figure 3) and by Wallman and Turke [8] using field-restricting blinders in the chicken. A recent paper by Hoyt et al [9] reported eight cases of monocular axial myopia in human infants associated with neonatal lid closure caused by third nerve palsy, eyelid disorders, or swelling of periorbital soft tissue due to obstetric trauma. A paper by Greene [10] reported on the investigation of possible mechanical factors involved in the production of axial myopia. With the upsurge of interest in myopia, an international research society recently has been formed, and major activity both in basic research and clinical investigation is beginning to appear.

Biochemists and mechanical engineers are beginning to study the development and prevention of refractive errors as the problems become better defined on a molecular and physical basis. In particular, biochemical investigation of aging changes in the crystalline lens may lead to better understanding of presbyopia and its possible prevention. Mechanical engineers are investigating imbalances in forces on the sclera that can lead to elongation of the eyeball and result in myopia, especially "progressive" myopia.

Clinical measurement of refractive errors or "clinical refraction," has progressed slowly over most of the past century. Clinical refraction is performed objectively or subjectively by various techniques. The basic method of objective refraction in the United States is retinoscopy, but manual

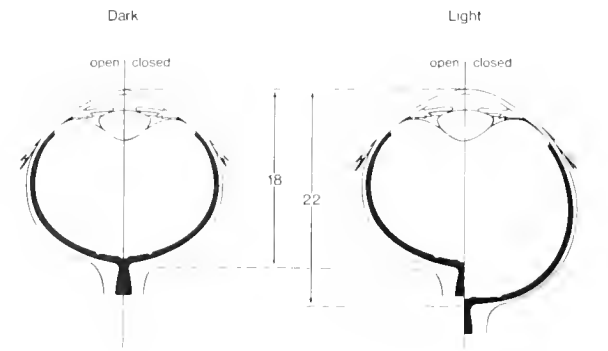

FIGURE 2. Neonatal lid fusion causes elongation of the eye globe in macaque monkeys when the animals are maintained in an illuminated environment. It has no effect on axial length when the monkeys are raised in the dark. The axial length of the eyes is expressed in milimeters. (Diagram on right reprinted from Wiesel TN, and Raviola E: *Invest Ophthalmol Vis Sci* 17:486, 1978.)

FIGURE 3. Tree shrews are promising new animal models that are being used to study myopia and its development. These animals, which develop myopia rapidly after monocular lid closure, are becoming more widely available through the development of breeding colonies. (Photograph courtesy of T. T. Norton.)

objective optometers have been used in other countries for many years. Photographic and visually evoked potential techniques have been developed recently for experimental use in objective refraction. Subjective methods of clinical refraction use responses from the patient to refine measurements, such as asking which lens provides better vision, "1 or 2." Present techniques are accurate but time-consuming and require a highly trained examiner.

Several commercial instruments for automated clinical refraction have appeared in the last ten years, but experience with the early instruments has emphasized the need to obtain reliable performance data before their use becomes widespread. Although automated refractors have been on the market since 1973, only one or two adequate clinical trials of a few of these instruments have been conducted. Ophthalmologists and optometrists in the United States have purchased approximately $50 million worth of these automated refractors without having the benefit of reliable performance data. Most of the early instruments did not perform as promised, are now obsolete, and represent an unfortunate cost passed on to the consumer. Although major improvements seem to have been made to the automated refractors, good clinical trials to assess their actual capabilities are still lacking. If these newer instruments perform as promised, it should now be possible to obtain a refractive measurement in less than 1.5 seconds, using any one of at least four different automated commercial instruments equipped with infrared light and computer-controlled electro-optical designs. In addition, automated subjective refractors have appeared which, if they live up to their promise, will at least equal the accuracy of conventional techniques of clinical refraction. Automatic keratometers, which are used for fitting contact lenses, are also being introduced, along with computerized devices for computing the optimal contact lens design for a given patient. Even now, little testing is being done on these instruments, in spite of the large number that is becoming commercially available.[11]

The design and dispensing of spectacle lenses for the correction of refractive errors has a strong scientific basis and has reached a high level of development through the pressures of commercial competition. Aspheric lenses for aphakia and progressive power lenses for presbyopia are now commonly available.

Correction of refractive errors involves either external optical correction, such as spectacle lenses or contact lenses, or surgical manipulation of the optical components, including changing or stabilizing the eyeball length.

The development of contact lenses for correcting refractive errors is still progressing rapidly. A variety of hard, semi-soft, soft, and "extended-wear" soft contact lenses are now available. A great deal has been learned about corneal physiology, and research on contact lenses is being performed mainly by corneal specialists. (See *Volume Two, Part Two, Report of the Corneal Diseases Panel*, Chapter 3).

Surgical correction of refractive errors has also developed rapidly in the past ten years. The implantation of intraocular lenses has become an accepted technique to treat aphakia, but it is not without risk. Various forms of refractive keratoplasty, surgical modification of the shape of the cornea to alter its refractive power, including keratoprostheses, keratomilieusis, keratophakia, epikeratophakia, and radial keratotomy, are still undergoing

investigation. (See *Volume Two, Part Two, Report of the Corneal Diseases Panel*, Chapter 3).

RESEARCH NEEDS AND OPPORTUNITIES

The factors involved in the control of eye growth, particularly in the average change in refractive error toward myopia between the ages of 6 and 30, are largely unknown. Heredity is clearly responsible for some forms of high refractive error. Heredity certainly plays a role in the development of ordinary refractive error as well and, according to prevalent opinion, probably plays the predominant role. Environmental influences have long been suspected[12] but have not yet been confirmed. Several population studies have attempted to identify specific hereditary or environmental influences on ordinary refractive error, but little useful or conclusive knowledge has been obtained, primarily because of failure to consider confounding variables.

Many methods have been proposed for preventing myopia, but most of them lack an experimental basis. For example, bifocals, with or without the use of cycloplegic drugs, have been proposed as a means of reducing or eliminating accommodation that may contribute to the progression of myopia in children. In addition, prism glasses have been proposed as a means of preventing myopia by eliminating convergence. Even with the recent use of clinical trials[13] evaluating these methods, they remain controversial.

Continued epidemiologic studies are needed to identify hereditary and environmental factors associated with the development of refractive errors. A number of questions should be addressed: Does accommodation and/or convergence associated with reading lead to axial myopia? Do unusual diets or climatic conditions favor the development of refractive errors? Which systemic diseases are associated with the development of refractive error? Does spectacle correction increase the progression of myopia? Are certain forms of glaucoma or strabismus associated with myopia? Which diseases of the eye and ocular adnexa affect the developmental size of the eyeball?

Continued refinement of animal models is needed for the study of refractive errors, especially myopia. Reliable animal models will allow testing of hypotheses relating to factors in the development and prevention of refractive errors.

Biochemical and electron microscopic analyses should be performed of scleral collagen from highly myopic eyes and compared with that from normal eyes to determine the factors that influence the mechanical strength and creep tendency of this material.

Further investigation of the forces exerted on the components of the eye is needed. Particularly, better techniques should be developed for measuring the forces exerted by the extraocular muscles under various conditions and in various directions of looking. Techniques should be developed for chronic in vivo measurement of intraocular pressure and of vitreous pressure.

Mechanical studies should be performed, both theoretical and experimental, of the stresses encountered in the posterior sclera, particularly in the vicinity of the optic nerve. The stresses and pressure increases involved in accommodation should be investigated, and accommodative behavior during normal seeing should be characterized in patients with and without refractive errors, using automatic, recording optometers.

Carefully controlled clinical trials should be performed, where appropriate, to evaluate proposed preventive measures for the development of myopia. For example, do cycloplegia or bifocals prevent or retard the progression of myopia?

Another refractive error of major concern is presbyopia. The crystalline lens hardens with age and the ciliary muscle atrophies, eventually eliminating active focusing by the eyes. The biochemical changes within the crystalline lens, as well as aging changes of the ciliary muscle, are poorly understood, and preventive measures remain only speculative. Thus, considerable basic research is needed before the factors that cause presbyopia can be elucidated.

Continued biochemical investigation of aging changes in the crystalline lens should be supported, with the ultimate aim of preventing or controlling the development of presbyopia. Physiological studies of aging changes of the ciliary muscle may also be useful. Techniques that would result in better optical compensation for presbyopia, especially dynamic compensation to allow active focusing, is an exciting area for investigation.

Although research in the measurement of refractive errors will progress largely through commercial channels, many instruments and techniques that are useful only for small populations of patients, such as refracting instruments for aphakic infants, may be ignored by industry because of the limited market. The developing and testing of such instruments should be supported by the NEI, and means should be explored for guiding the resources of industry toward developing useful, if not commercially attractive, refracting instrumentation. Independent testing programs for refracting instruments should be actively supported; direct regulation should be avoided and evaluation and dissemination of results encouraged.

Finally, the development of methods of mass screening for refractive errors should be actively supported.

RECOMMENDATIONS

Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in "Optics and Refractive Errors, Including Myopia," the Panel has made the following recommendations concerning research in this subprogram over the next five years. These have all been designated as Program Development Priorities and include areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these areas are forthcoming.

Program Development Priorities

- Study the etiology and mechanisms of myopia, using both animal models and physiochemical approacnes.
- Conduct epidemiological studies of risk factors for myopia, as well as limited, well-designed clinical trials, of available treatments for myopia.
- Develop and test special-purpose refracting instruments, especially those not likely to be developed by industry.
- Develop valid and reliable methods for mass screening for refractive errors.

RESOURCE REQUIREMENTS

After reviewing current research grant support in each of these categories and assessing the need and potential for future development, the Panel has estimated the number of projects it believes are needed to carry out its recommendations in FY 1983. These estimates are shown in the table on the following page. For a discussion of the general basis and significance of these projections, see the "Summary" at the beginning of this report.

RESOURCE TABLE

OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA

OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA

	No. of Grants FY 1981	Panel Recommendation FY 83	
		Add. Grants	Total Grants
Program Development Priorities			
A. Study myopia using animal models and physiochemical approaches.	3	4	7
B. Conduct epidemiological studies of risk factors for myopia and clinical trials of treatments for myopia.	0	2	2
C. Develop/test special purpose refracting instruments.	0	2	2
D. Develop mass screening methods for refractive errors.	0	1	1
Subtotal Grants	**3**	**9**	**12**
(% of Program)	**(1)**	**(10)**	**(3)**
Total Estimated Cost	**$261,000**	**$915,000**	**$1,176,000**

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